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## CONTENTS

### NEW SERIES, VOLUME 7, NUMBER 25, JANUARY 1938

A Type of Gonococcal Bacteraemia with Characteristic Haemorrhagic Vesiculo-pustular and Bullous Skin Lesions. By Harry Keil. With Plates 1 and 2 . . . . .	1
Insulin Resistance in Diabetes Mellitus and the Effect of Dietary Carbohydrate. By O. L. V. de Wesselow and W. J. Griffiths . . . . .	17
Over-stimulation of the Vagus Nerve in Rheumatic Fever. By J. D. Keith . . . . .	29
Some Rare Types of Macrocytic Anaemia. By L. S. P. Davidson and H. W. Fullerton . . . . .	43
The Radiology of Pulmonary Infarction. By K. Shirley Smith. With Plates 3 to 6 . . . . .	85
The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Haemolytic Anaemia. By R. Bodley Scott, A. H. T. Robb-Smith, and E. F. Scowen. With Plates 7 and 8 . . . . .	95
Hyperinsulinism Due to a Pancreatic Islet Adenoma. By Russell Fraser, W. S. MacLay, and S. A. Mann. With Plate 9 . . . . .	115
Haemolytic (Spherocytic) Jaundice in the Adult. By M. C. G. Israëls and John F. Wilkinson. With Plates 10 and 11 . . . . .	137
The Anterior Pituitary Lobe in Graves' Disease and in Myxoedema. By Cuthbert Leslie Cope . . . . .	151

### NUMBER 26, APRIL 1938

A Preliminary Report on the Value of Stock Vaccine in the Treatment of Pneumonia. By J. H. Bolton . . . . .	171
Hypogonadism Associated with Invasion of the Mid-brain and Hypothalamus by a Pineal Tumour. By R. A. Cleghorn, H. H. Hyland, J. R. F. Mills, and E. A. Linell. With Plates 12 to 15 . . . . .	183
Myelomatosis. By Alice Stewart in collaboration with F. Parkes Weber. With Plates 16 to 18 . . . . .	211
Some Observations on the Laevulose Tolerance Test. By C. P. Stewart, Harold Scarborough, and J. N. Davidson . . . . .	229
Tuberculous Splenomegaly, with Miliary Tuberculosis of the Lungs. By R. A. Hickling. With Plates 19 and 20 . . . . .	263
Insulin Antagonism. By Alexander Glen and James Caithness Eaton . . . . .	271
Exophthalmic Ophthalmoplegia. By W. Russell Brain. (With a Pathological Report on the Ocular Muscles and Thyroid Glands by Hubert M. Turnbull). With Plates 21 to 23 . . . . .	293
Familial Idiopathic Methaemoglobinaemia. By E. H. Bensley, L. J. Rhea, and E. S. Mills . . . . .	325

## NUMBER 27, JULY 1938

The Output of the Heart in Congestive Failure. By John McMichael . . .	331
The Clinical Value of the Estimation of Laevulose Tolerance by Means of Analyses of Blood-laevulose. By Freda K. Herbert and George Davison . . . . .	355
Pulmonary Tuberculosis complicating Diabetes Mellitus. By H. P. Hims-worth. With Plates 24 to 26 . . . . .	373
The Role of Copper in Iron-deficiency Anaemia in Infancy. By James H. Hutchison . . . . .	397
Dyspnoea: A Review. By Ronald V. Christie . . . . .	421
Cardiac Aneurysm. By John Parkinson, D. Evan Bedford, and W. A. R. Thomson. With Plates 27 to 31 . . . . .	455
The Genetics of Transposition of the Viscera. By E. A. Cockayne . . .	479

## NUMBER 28, OCTOBER 1938

Anaemia in Myxoedema: and the Role of the Thyroid Gland in Erythropoiesis. By Richard Bomford . . . . .	495
Staphylococcal Infections at Singapore. By William Hughes . . . . .	537
The Haemopoietic Activity of the Human Stomach in Pernicious Anaemia. By John Frederick Wilkinson, Louis Klein, and Charles Amos Ashford . . .	555
An Investigation into the Treatment of Parkinsonism with Bulgarian Belladonna. By N. S. Alcock and E. Arnold Carmichael. With Plate 32 . . .	565
Observations on the Relation of Leucocytosis to Ascorbic Acid Requirements. By Tracy D. Cuttle . . . . .	575
Proceedings of the Association of Physicians of Great Britain and Ireland. 1938. Thirty-second Annual General Meeting . . . . .	585

## INDEX OF CONTRIBUTORS

ALCOCK, N. S. An Investigation into the Treatment of Parkinsonism with Bulgarian Belladonna. With Plate 32 . . . . .	565
ASHFORD, C. A. The Haemopoietic Activity of the Human Stomach in Pernicious Anaemia . . . . .	555
BEDFORD, D. E. Cardiac Aneurysm. With Plates 27 to 31 . . . . .	455
BENSLEY, E. H. Familial Idiopathic Methaemoglobinaemia . . . . .	325
BOLTON, J. H. A Preliminary Report of the Value of Stock Vaccine in the Treatment of Pneumonia . . . . .	171
BOMFORD, R. Anaemia in Myxoedema: and the Role of the Thyroid Gland in Erythropoiesis . . . . .	495
BRAIN, W. R. Exophthalmic Ophthalmoplegia. With Plates 21 to 23 . . . . .	293
CARMICHAEL, E. A. An Investigation into the Treatment of Parkinsonism with Bulgarian Belladonna. With Plate 32 . . . . .	565
CHRISTIE, R. V. Dyspnoea: A Review . . . . .	421
CLEGHORN, R. A. Hypogonadism Associated with Invasion of the Mid-brain and Hypothalamus by a Pineal Tumour. With Plates 12 to 15 . . . . .	183
COCKAYNE, E. A. The Genetics of Transposition of the Viscera . . . . .	479
COPE, C. L. The Anterior Pituitary Lobe in Graves' Disease and in Myxoedema . . . . .	151
CUTTLE, T. D. Observations on the Relation of Leucocytosis to Ascorbic Acid Requirements . . . . .	575
DAVIDSON, J. N. Some Observations on the Laevulose Tolerance Test . . . . .	229
DAVIDSON, L. S. P. Some Rare Types of Macrocytic Anaemia . . . . .	43
DAVISON, G. The Clinical Value of the Estimation of Laevulose Tolerance by Means of Analyses of Blood-laevulose . . . . .	355
DE WESSELOW, O. L. V. Insulin Resistance in Diabetes Mellitus and the Effect of Dietary Carbohydrate . . . . .	17
EATON, J. C. Insulin Antagonism . . . . .	271
FRASER, R. Hyperinsulinism Due to a Pancreatic Islet Adenoma. With Plate 9 . . . . .	115
FULLERTON, H. W. Some Rare Types of Macrocytic Anaemia . . . . .	43
GLEN, A. Insulin Antagonism . . . . .	271
GRIFFITHS, W. J. Insulin Resistance in Diabetes Mellitus and the Effect of Dietary Carbohydrate . . . . .	17
HERBERT, F. K. The Clinical Value of the Estimation of Laevulose Tolerance by Means of Analyses of Blood-laevulose . . . . .	355
HICKLING, R. A. Tuberculous Splenomegaly, with Miliary Tuberculosis of the Lungs. With Plates 19 and 20 . . . . .	263
HIMSWORTH, H. P. Pulmonary Tuberculosis complicating Diabetes Mellitus. With Plates 24 to 26 . . . . .	373
HUGHES, W. Staphylococcal Infections at Singapore . . . . .	537
HUTCHISON, J. H. The Role of Copper in Iron-deficiency Anaemia in Infancy . . . . .	397
HYLAND, H. H. Hypogonadism Associated with Invasion of the Mid-brain and Hypothalamus by a Pineal Tumour. With Plates 12 to 15 . . . . .	183

ISRAËLS, M. C. G. Haemolytic (Spherocytic) Jaundice in the Adult. With Plates 10 and 11 . . . . .	137
KEIL, H. A Type of Gonococcal Bacteraemia with Characteristic Haemorrhagic Vesiculo-pustular and Bullous Skin Lesions. With Plates 1 and 2 . . . . .	1
KEITH, J. D. Over-stimulation of the Vagus Nerve in Rheumatic Fever . . . . .	29
KLEIN, L. The Haemopoietic Activity of the Human Stomach in Pernicious Anaemia . . . . .	555
LINELL, E. A. Hypogonadism Associated with Invasion of the Mid-brain and Hypothalamus by a Pineal Tumour. With Plates 12 to 15 . . . . .	183
MACLAY, W. S. Hyperinsulinism Due to a Pancreatic Islet Adenoma. With Plate 9 . . . . .	115
MCMICHAEL, J. The Output of the Heart in Congestive Failure . . . . .	331
MANN, S. A. Hyperinsulinism Due to a Pancreatic Islet Adenoma. With Plate 9 . . . . .	115
MILLS, E. S. Familial Idiopathic Methaemoglobinaemia . . . . .	325
MILLS, J. R. F. Hypogonadism Associated with Invasion of the Mid-brain and Hypothalamus by a Pineal Tumour. With Plates 12 to 15 . . . . .	183
PARKINSON, J. Cardiac Aneurysm. With Plates 27 to 31 . . . . .	455
Proceedings of the Association of Physicians of Great Britain and Ireland. 1938. Thirty-second Annual General Meeting . . . . .	585
RHEA, L. J. Familial Idiopathic Methaemoglobinaemia . . . . .	325
ROBB-SMITH, A. H. T. The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Haemolytic Anaemia. With Plates 7 and 8 . . . . .	95
SCARBOROUGH, H. Some Observations on the Laevulose Tolerance Test . . . . .	229
SCOTT, R. B. The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Haemolytic Anaemia. With Plates 7 and 8 . . . . .	95
SCOWEN, E. F. The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Haemolytic Anaemia. With Plates 7 and 8 . . . . .	95
SMITH, K. S. The Radiology of Pulmonary Infarction. With Plates 3 to 6 . . . . .	85
STEWART, A. Myelomatosis. With Plates 16 to 18 . . . . .	211
STEWART, C. P. Some Observations on the Laevulose Tolerance Test . . . . .	229
THOMSON, W. A. R. Cardiac Aneurysm. With Plates 27 to 31 . . . . .	455
TURNBULL, H. M. Pathological Report on the Ocular Muscles and Thyroid Glands in Exophthalmic Ophthalmoplegia. With Plates 21 to 23 . . . . .	293
WEBER, F. P. Myelomatosis. With Plates 16 to 18 . . . . .	211
WILKINSON, J. F. Haemolytic (Spherocytic) Jaundice in the Adult. With Plates 10 and 11 . . . . .	137
— The Haemopoietic Activity of the Human Stomach in Pernicious Anaemia . . . . .	555

## INDEX

- Adenoma, pancreatic islet, hyperinsulinism due to a, 115.
- Adrenaline, effect of, on the P-R interval in rheumatic heart disease, 35.
- Air, rarefied, inhalation of, associated with dyspnoea, 447.
- Anaemia, haemolytic, the Marchiafava-Micheli syndrome of nocturnal haemoglobinuria with, 95.
- Anaemia in myxoedema, 495.
- Anaemia, iron-deficiency, in infancy, role of copper in, 397; mode of action of copper in, 401.
- Anaemia, macrocytic, some rare types of, 43.
- Anaemia, pernicious, haemopoietic activity of human stomach in, 555.
- Anaemias, treatment of, use of thyroid in, 528.
- Aneurysm, cardiac, 455; of anterior wall of the left ventricle, 464.
- Anterior pituitary lobe in Graves' disease and in myxoedema, 151.
- Atropine, effect of, on the P-R interval in rheumatic heart disease, 33.
- Ascorbic acid requirements, relation of leucocytosis to, 575.
- Bacteraemia, gonococcal, with characteristic haemorrhagic vesiculo-pustular and bullous skin lesions, a type of, 1; differential diagnosis of skin lesions, 12.
- Belladonna, Bulgarian, treatment of Parkinsonism with, 565.
- Blood, diseases of, associated with dyspnoea, 428.
- Brain, mid-, invasion of, by a pineal tumour, hypogonadism associated with, 183; influences causing failure of secretion of the gametogenic hormone, 199; neuro-humoral regulation of gonadotropic hormone secretion, 202.
- Bulgarian belladonna, treatment of Parkinsonism with, 565.
- Cardiac aneurysm, 455.
- Circulatory system, diseases of, associated with dyspnoea, 428.
- Copper, role of, in iron-deficiency anaemia in infancy, 397; mode of action of, 401.
- Diabetes mellitus, insulin resistance in, and the effect of dietary carbohydrate, 17; pulmonary tuberculosis complicating, 373; diagnosis and association of, and pulmonary tuberculosis, 375; association of, and pulmonary tuberculosis, 383; treatment of, 385.
- Dyspnoea, 421; definition of, 422; causes of, 423; types of, 425; conditions commonly associated with, 428.
- Erythropoiesis, role of thyroid gland in, 520; review of observations on the bone-marrow, 524; use of thyroid in treatment of anaemias, 528.
- Exophthalmic ophthalmoplegia, 293; other muscular disorders associated with thyrotoxicosis, 309.
- Familial idiopathic methaemoglobinaemia, 325.
- Gases, foreign, inhalation of, associated with dyspnoea, 446.
- Gonococcal bacteraemia with characteristic haemorrhagic vesiculo-pustular and bullous skin lesions, a type of, 1; differential diagnosis of skin lesions, 12.
- Graves' disease, anterior pituitary lobe in, and in myxoedema, 151.
- Haemoglobinuria, nocturnal, with haemolytic anaemia, Marchiafava-Micheli syndrome of, 95.
- Haemolytic anaemia, the Marchiafava-Micheli syndrome of nocturnal haemoglobinuria with, 95.
- Haemolytic (spherocytic) jaundice in the adult, 137.
- Haemopoietic activity of the human stomach in pernicious anaemia, 555.
- Heart, output of, in congestive failure, 331; postural changes in heart output and heart-rate, 333; determination of cardiac output in heart failure, 336.
- Heart disease, rheumatic, effect of atropine on the P-R interval in, 33; effect of adrenaline on the P-R interval in, 35.
- Heart failure, determination of cardiac output in, 336.
- Heart-rate, postural changes in heart output and, 333.
- Hyperinsulinism due to a pancreatic islet adenoma, 115.
- Hypogonadism associated with invasion of the mid-brain and hypothalamus

- by a pineal tumour, 183; influences causing failure of secretion of the gametogenic hormone, 199; neuro-humoral regulation of gonadotropic hormone secretion, 202.
- Hypothalamus, invasion of, by a pineal tumour, hypogonadism associated with, 183; influences causing failure of secretion of the gametogenic hormone, 199; neuro-humoral regulation of gonadotropic hormone secretion, 202.
- Idiopathic methaemoglobinaemia, familial, 325.
- Infarction, pulmonary, radiology of, 85.
- Insulin antagonism, 271.
- Insulin resistance in diabetes mellitus and the effect of dietary carbohydrate, 17.
- Jaundice, haemolytic (spherocytic), in the adult, 137.
- Laevulose tolerance, clinical value of estimation of, by means of analyses of blood-laevulose, 355.
- Laevulose tolerance test, some observations on, 229.
- Leucocytosis, relation of, to ascorbic acid requirements, 575.
- Lungs, diseases of, associated with dyspnoea, 439.
- Macrocytic anaemia, some rare types of, 43.
- Marchiafava-Micheli syndrome of nocturnal haemoglobinuria with haemolytic anaemia, 95.
- Metabolism, disturbances of, associated with dyspnoea, 444.
- Methaemoglobinaemia, idiopathic, familial, 325.
- Myelomatosis, 211.
- Myxoedema, anterior pituitary lobe in Graves' disease and in, 151; anaemia in, 495.
- Nervous system, disorders of, associated with dyspnoea, 445.
- Ophthalmoplegia, exophthalmic, 293; other muscular disorders associated with thyrotoxicosis, 309.
- Pancreatic islet adenoma, hyperinsulinism due to a, 115.
- Parkinsonism, treatment of, with Bulgarian belladonna, 565.
- Pituitary lobe, anterior, in Graves' disease, and in myxoedema, 151.
- Pleura, diseases of, associated with dyspnoea, 439.
- Pneumonia, staphylococcal, 545.
- Pneumonia, treatment of, preliminary report on the value of stock vaccine in, 171.
- Pulmonary infarction, radiology of, 85.
- Radiology of pulmonary infarction, 85.
- Rheumatic fever, over-stimulation of vagus nerve in, 29; auriculo-ventricular conduction time in normal children, 29; auriculo-ventricular conduction in children suffering from rheumatic fever, 30; effect of atropine on the P-R interval in rheumatic heart disease, 33; effect of adrenaline on the P-R interval in rheumatic heart disease, 35; pulse-rate, 37; abdominal pain and vomiting, 39.
- Rheumatic heart disease, effect of atropine on the P-R interval in, 33; effect of adrenaline on the P-R interval in, 35.
- Splenomegaly, tuberculous, with miliary tuberculosis of the lungs, 263.
- Staphylococcal infections at Singapore, 537; boils and associated lesions 538; scalp infections in Chinese children, 541; pemphigus contagiosus, 543; staphylococcal pneumonia and lung abscess, 545; pyomyositis, 546.
- Stomach, human, haemopoietic activity of, in pernicious anaemia, 555.
- Thyroid gland, role of, in erythropoiesis, 520; review of observations on the bone-marrow, 524; use of thyroid in treatment of anaemias, 528.
- Thyrotoxicosis, muscular disorders associated with, 309.
- Tuberculosis, pulmonary, complicating diabetes mellitus, 373; diagnosis and association of, and diabetes mellitus, 375; association of diabetes and, 383; treatment of, 391.
- Tuberculous splenomegaly, with miliary tuberculosis of the lungs, 263.
- Vagus nerve, over-stimulation of, in rheumatic fever, 29; auriculo-ventricular conduction time in normal children, 29; auriculo-ventricular conduction in children suffering from rheumatic fever, 30; effect of atropine on the P-R interval in rheumatic heart disease, 33; effect of adrenaline on the P-R interval in rheumatic heart disease, 35; pulse-rate, 37; abdominal pain and vomiting, 39.
- Viscera, transposition of, genetics of, 479.

A TYPE OF GONOCOCCAL BACTERAEMIA WITH  
CHARACTERISTIC HAEMORRHAGIC VESICULO-  
PUSTULAR AND BULLOUS SKIN LESIONS<sup>1</sup>

By HARRY KEIL

(New York City)

With Plates 1 and 2

THIS report concerns a form of gonococcal bacteraemia in which the patients often appear to be profoundly ill and in which the initial clinical impression seems consistent with a poor or guarded prognosis. This belief is strengthened when there are cardiac murmurs and the blood cultures are positive. Despite this, recovery is the rule. The course of these cases is often explained on the basis of healed gonococcal endocarditis accompanied by haemorrhagic skin lesions, but my observations are at variance with this hypothesis. In support of my thesis, it is proposed: (1) to cite five illustrative examples of this variety of bacteraemia, accompanied by this singular eruption: (2) to attempt to establish the significance of the skin lesions in relation to the clinical picture with which they are associated; (3) to contrast the features of this condition with those seen in gonococcal endocarditis. Although the literature contains isolated reports of this dermatosis, it appears that its diagnostic value has not been sufficiently recognized (Cabot, 1927) and that in many instances the skin lesions have been regarded as either a simple pyoderma, a drug eruption, a variant of 'erythema multiforme' or as a non-specific 'toxic' manifestation.

*Report of Cases*

*Case 1.* The patient, a woman aged 30, was first seen in the early part of 1932. Two months after marriage or nine years before the present observation, she had an attack of pain in the left ankle. The affected area became red, swollen, and tender to touch, the condition lasting four months. Following this, the tonsils were removed. She was gravid three times, the last child having been born four months before the present illness. About three months later she noted increasing pain in the left knee and right wrist. This was accompanied by fever, at times reaching a peak of 102° F., and occasionally associated with chills(?). On the day before admission, 'pimples' appeared on the distal parts of the limbs, the lesions being heralded by a drawing sensation. Redness occurred at the sites, followed by the formation of blisters, the centres of which speedily became coloured 'black'. The patient stated that she had experienced ten shaking chills during the day, a piece of information regarded as of doubtful authenticity.

<sup>1</sup> Received June 5, 1937.

On examination she appeared acutely ill. The temperature was 102° F.; the pulse-rate 124. The left knee-joint was slightly tender, with some pain on motion, but without obvious swelling. The right wrist, hand, and fingers were sites of a diffuse inflammatory process; the affected parts revealed pitting oedema, warmth, and tenderness to touch, while the overlying skin had a cyanosed hue. There was also impaired mobility. The left elbow was warm and tender to touch, with pain on active and passive motion. The skin of the upper and lower limbs showed scattered lesions, located chiefly on their distal parts; there was no definite predilection for either the flexor or extensor aspects. Those of recent origin were erythematopapular and slightly indurated; a few of them contained vesicular and pustular centres. The older lesions were slightly larger and characterized by central haemorrhagic vesicles and bullae coloured bluish-black. Some of the latter lesions had collapsed to form crusts. Puncture of a bulla disclosed thin serous purulent fluid, examination of which failed to show organisms on direct smear and culture. There was a soft blowing systolic murmur at the apex of the heart; the second pulmonary sound was louder than the second aortic sound, but it was not accentuated. The rhythm was regular. There were no thrills. A pelvic examination showed no abnormalities. The haemoglobin was 63 per cent.; the white-blood cells numbered 16,500 with 80 per cent. polymorphonuclear leucocytes: the platelet count was 250,000. Cervical and urethral smears revealed no gonococci. Subsequent gynaecological examinations disclosed no abnormalities. A few small vesicles, surrounded by an erythematous halo, were observed on the soft palate. Several days later the right wrist and hand assumed an appearance commonly seen in a gonococcal infection; smear and culture of fluid obtained from the right wrist and from a pustular lesion showed no organisms. During the succeeding week the temperature ranged from between 102° F. to 103° F., without the occurrence of chills or fresh crops of skin lesions. The gonococcus complement fixation reaction was negative. In view of a history of arthritis some nine years before this observation, the absence of cardiac involvement and the normal electrocardiograms appeared to militate against the diagnosis of rheumatic fever. In the interim the blood culture revealed a Gram-negative diplococcus identified as the gonococcus. The possibility of gonococcal endocarditis was conjectured at this time, but this belief seemed to be disproved by subsequent events.

Several cubic centimetres of turbid fluid were aspirated from the left elbow-joint. Smear showed numerous pus cells with many Gram-negative extra- and intra-cellular diplococci considered as typical of gonococci; this was corroborated by culture. There was now elicited from the patient's husband the information that he had suffered an attack of gonorrhoeal urethritis four months previously and that he had had sexual intercourse with his wife during the subacute stage of the disease.

The last pelvic examination made about one month after the initial observation still disclosed no abnormalities. At this time, also, a blood culture was sterile. Examination of urinary sediment had revealed no more than an occasional white-blood cell and a rare hyaline cast. Because of the occasional articular pains, gonococcal vaccine was given intramuscularly, commencing with 100 million units and gradually increasing the dose to 1-1/2 billion units. The temperature fell to normal and the patient was sent home.

More than a year later examination of the heart and the articulation disclosed no abnormal findings.

*Comment.* Although a local focus of gonorrhoeal infection was not found, the history of recent disease in the husband and the cultivation of the organism from the blood-stream and a joint appeared to substantiate this diagnosis. The spread of the condition after pregnancy is a not uncommon event. It is likely that the patient had contracted gonorrhoea some nine years ago (two months after marriage) and that the disease had expressed itself chiefly in the form of an attack of arthritis, without evidence of menstrual disturbances, leucorrhoea, or other local signs. No particular significance was attributed to the eruption owing to unfamiliarity with it. Although the gonococcus was not isolated from the skin lesions, it seemed probable, retrospectively, that they had been caused by haematogenous invasion of the organism, and subsequent observations to be detailed appeared to substantiate this inference. That the bacteraemia was transient was shown by the clinical course and the last sterile blood culture. The equivocal cardiac signs in association with haemorrhagic skin lesions and the initial positive blood culture suggested the diagnosis of gonococcal endocarditis. The tendency to attribute the cure to the use of gonococcal vaccine requires evaluation in the light of the spontaneous recoveries seen in this condition. Finally, an examination made over one year later revealed no residual sequelae in the joints.

*Case 2.* Six days after discharge of the first patient, there came under observation a boy aged 16, presenting a similar condition. Four weeks before, he experienced difficulty in starting the urinary stream in the presence of a full bladder; this was accompanied by burning on micturition. Three weeks later he noted a bead of pus at the tip of the penis, and, shortly after, the left ankle became swollen, red, and painful. He complained of sore throat, difficulty in swallowing, and palpitations of the heart. He felt feverish and had chilly sensations. Then the right shoulder and the terminal joint of the middle finger of the left hand became swollen, hot, and painful. No history of sexual exposure was elicited at this time.

On examination he appeared acutely ill. The temperature was 102° F.; the pulse-rate 120. The left ankle and the distal phalanx of the middle finger of the left hand were swollen and tender, the overlying skin presenting a reddish glistening appearance. The right shoulder was not swollen, but there was restriction of active and passive motion. Examination of the heart disclosed no abnormalities of note; the second pulmonary sound was louder than the second aortic sound, but it was not accentuated. The haemoglobin was 96 per cent.; the white-blood cell count 12,250 with 79 per cent. polymorphonuclear leucocytes. The diagnosis of acute rheumatic fever was suggested.

Two days later there appeared, for the first time, two erythematous haemorrhagic bullae, one situated over the knuckle of the left index finger, the other on the outer aspect of the right foot near the small toe. They were slightly tender and moderately indurated (oedema?). The lesion on the foot showed a central purplish-black haemorrhagic bulla, 1/16 in. in diameter, which was surrounded by a narrow zone of pallor, in turn encircled by an area of indurated erythema. The lesion on the hand was almost identical in appearance, except that the haemorrhagic centre was not as sharply circumscribed and the intermediary zone of pallor was lacking.

Bearing the first case in mind, it appeared that the attributes of the skin lesions, type of arthropathy, and history of urethritis favoured the diagnosis of gonococcal infection. However, the denial of sexual exposure by this young patient, the onset with sore throat and migratory polyarthritides, and the history of palpitations suggested rheumatic fever as the aetiology of the condition. Those who considered the skin lesions as non-specific pointed out that they had appeared when the temperature was normal and that their occurrence had neither been preceded nor followed by fever. Others regarded the eruption as small furuncles, probably of staphylococcal origin. The sedimentation time (Linzenmaier method) was 48 minutes.

Subsequently, the polyarthritides became more intense, with spread to other joints. The bullae assumed a pustular appearance. Aspiration of these lesions revealed purulent fluid, microscopic examination showing numerous pus cells but no organisms. However, a Gram-negative diplococcus with the morphology of the gonococcus was isolated on culture of the contents of a skin lesion, but there was insufficient growth for agglutination tests. Two cubic centimetres of cloudy fluid were aspirated from the left ankle-joint; on direct smear several pairs of Gram-negative intracellular diplococci were found, identified culturally as the gonococcus. Three cultures of blood were sterile. The use of sodium salicylate seemed to exert no beneficial effect on the course of the polyarthritides. Several electrocardiograms revealed no definite abnormalities. The haemoglobin diminished to 76 per cent.

It was now learned that the patient had acquired gonorrhoea some six months before. A gonococcus complement fixation reaction was negative. The affection of the shoulder and finger-joints subsided, but the left ankle remained considerably swollen, red, and tender. It was treated by immobilization in a cast, and the patient was given a course of artificial fever therapy induced by diathermy. Following this, the pain subsided and the swelling and tenderness disappeared gradually. However, some limitation in the movement of the joint remained. As soon as immobilization was discontinued, the range of movement steadily increased and, when last seen, mobility of the left ankle, though still impaired, was much improved.

About six months later the patient was seen a second time during a typical attack of lobar pneumonia, from which he recovered. The left ankle was stiff at an angle of 90 degrees. The gonococcus complement fixation reaction was still negative.

*Comment.* Although there was but a single crop of skin lesions, their morphology recalled the eruption observed in the first case. The clinical picture resembled rheumatic fever. However, bullous lesions, particularly of the haemorrhagic type, are rarely, if ever, encountered in the rheumatic affection (Keil, 11), the few recorded cases of this association seem not to possess the stamp of authenticity, if analysed in terms of modern criteria. Although organisms were not found on direct smear of the contents of a bulla, culture revealed a small number of colonies of a Gram-negative diplococcus, resembling the gonococcus in its typical morphological features. Despite the three sterile cultures of blood, the haematogenous dissemination of the organism seemed probable in view of its isolation from the aspirated fluid of the left ankle-joint and the contents of a bulla.

*Case 3.* About six months after the observation of the second patient,

another similar case was seen in a man aged 37. At the age of 24 he contracted acute gonorrhoea, accompanied by 'roseola'. After a lapse of nine years he acquired gonorrhoea a second time. One week before the present observation he complained of chilly sensations, vague muscular pains, slight sore throat, and painful swelling of the right heel. On the following day the right wrist became swollen, red, and painful. A transient eruption composed of small reddish spots appeared on the forearms and left shoulder. During the period of observation of two weeks, the temperature was subfebrile. The patient complained of pains in various joints. There was moderate hepato-splenomegaly attributed to a previous attack of malaria. Examination of the heart revealed no abnormalities. The skin was free of eruption. A gonococcus complement fixation reaction was negative. Prostatic massage failed to yield secretion for study. An electrocardiogram showed no alterations. A diagnosis of acute infectious arthritis was suggested. The tonsils were removed and two teeth extracted. The arthritis subsided. A Wassermann test was positive (four plus) and anti-syphilitic treatment was therefore advised.

Over a year later the patient was seen again. He had been receiving specific therapy. There had been no recurrence of the gonorrhoeal infection. Three days before, he had a transient attack of colic. Two days later he complained of pain over the outer aspect of the right foot; there was no redness or swelling of the part. Several hours later painful areas appeared in the mid-thigh regions. The following day the right foot seemed improved but there was a feeling of discomfort in the knee-joints posteriorly. The temperature rose sharply to 104° F. and the patient complained of a sense of chilliness. Tender small red spots appeared over the styloid process of the right ulna and on the volar aspect of the left forearm.

On examination he appeared acutely ill. The temperature was 101.6° F.; the pulse-rate only 80. The cardiac condition was normal. Scattered over the arms, forearms, chest, abdomen, and lower limbs were numerous erythematous-macular and papular discrete lesions, some of which had pustular centres. On the right forearm there was a haemorrhagic bulla encircled by a narrow whitish ring, which, in turn, was surrounded by an erythematous border fading imperceptibly into normal skin. The diagnosis of gonococcal bacteraemia was made. On the following day, the temperature rose to 104.2° F. Cultures of blood and of a pustule were sterile. The next day there appeared on the volar surface of the right index finger a fresh skin lesion showing a dark centre (haemorrhage) with surrounding erythema. The temperature had now fallen to 99.4° F. Examination of a pustular lesion revealed numerous pus cells on direct smear but no organisms. The temperature remained normal for the remainder of the course.

*Comment.* Although the gonococcus was not isolated either in culture of blood or skin lesion, the concept of a relatively transient benign gonococcal bacteraemia appeared to explain reasonably the clinical course. There had been two antecedent attacks of gonorrhoea. It seemed likely that the polyarthritis observed during the first admission was also of gonococcal origin. The morphology of the eruption was similar to that observed in the two instances previously described. The association of numerous pus cells in the skin lesions with absence of demonstrable organisms is commonly found in these cases, whereas the causative agent is, as a rule, easily demonstrated in other 'metastatic dermatoses'.

*Case 4.* In the interim between the two observations in Case 3, a typical example of the condition was seen in a married woman aged 36. Two months before the present illness, the menses ceased abruptly, continuing in this state for the succeeding eight months. Following a gynaecological examination she had a profuse haemorrhage lasting several hours. After this, amenorrhoea set in again. There was no vaginal discharge. Venereal infection was denied. Nine days before observation there was a rapid onset of generalized myalgia and arthralgia, accompanied by slight fever; the pains were dull, irregular, and transient. At the same time many small pustules appeared on the extremities, the greater part of the eruption disappearing in a short time. The left knee began to swell, and a few days later several ounces of turbid yellow fluid were removed from it. There were no chills.

On examination the patient appeared acutely ill. The temperature was 101.8° F.; the pulse-rate 96. The cardiac condition was normal; the second pulmonary sound was louder than the second aortic sound. About the left elbow were two crusted erythematous lesions, one of which was covered by a pustular bleb (Plate 1, Fig. 1). There were scattered haemorrhagic vesicles and bullae on the limbs (Plate 1, Fig. 2), notably on the fingers. Some observers regarded the eruption as an unusual variety of 'erythema multiforme'. The left knee-joint was swollen and tender, with marked restriction in mobility. The haemoglobin was 74 per cent.; the white-blood cell count 9,100, with 79 per cent. polymorphonuclear leucocytes. The Wassermann test was negative. The sedimentation time was seventeen minutes. Smear of the contents of a pustule on the right ankle revealed numerous pus cells and several pairs of Gram-negative intracellular biscuit-shaped diplococci, probably gonococci. Culture of a skin lesion, made several days later, showed only a contaminating *Staphylococcus albus*. Gynaecological examination disclosed no abnormalities. Recalling the previous observations, the diagnosis of gonococcal septicaemia was entertained. Other observers suggested the possibility of chronic meningococcal bacteraemia. A blood culture was sterile.

Two days later a fresh haemorrhagic vesicle appeared over the left knee. Roentgenograms of this area revealed no changes in the bones, but there was pronounced fullness in the region of the subquadriceps bursa. Ten cubic centimetres of cloudy fluid were aspirated from the suprapatellar bursa; smear of the contents showed a Gram-negative diplococcus identified by culture as the gonococcus. A gonococcus complement fixation reaction was negative. Subsequently, the left knee was treated by traction in the extended position and the patient given a course of hyperthermia. Although the affected part was considerably improved, it could not be flexed to any extent without causing pain. During the first three weeks the temperature ranged from between 100° F. and 103° F., then became subfebrile. Two electrocardiograms showed no abnormalities.

Four months after discharge examination revealed that the left knee could be flexed to an angle of 45 degrees. She was exercising the affected part moderately and receiving baking treatments.

*Comment.* It seems curious that in the cases thus far described the gonococcus complement fixation reactions were negative. Considering the high incidence of positive results recorded in the literature on systemic gonococcal infections, it appears difficult to explain the difference, unless it

can be attributed to the use of a relatively less sensitive method or an unusual run of cases.

*Case 5.* Just before the fourth patient was discharged, another example of the condition was encountered in a man 23 years of age. The illness began four months before, when he contracted gonorrhoeal urethritis. Following intensive treatment with irrigations and prostatic massage for many weeks, he was discharged by his private physician as cured. About a fortnight later he was awakened by pain in the right shoulder and right calf, accompanied by generalized aches and pains. He felt chilly and perspired profusely. The following day he had 'sore pain' in the right forearm and left thumb, succeeded by similar discomfort in both mid-thigh regions. Four days after the onset of this illness the arch of the right foot and the corresponding fourth toe became inflamed, with swelling and a broad area of erythema over the dorsum of the affected parts. The following day the opposite foot was similarly involved. The erythematous area on the right foot was incised. The pain affected the feet alternately, without spreading to other joints. The diagnosis of gonococcal arthritis was now suggested. Gonococcal vaccine was administered subcutaneously, with the production of intense sweating but no relief of the symptoms. Shortly before admission there appeared on the dorsum of the left wrist a small erythematous lesion that was painful to touch.

On examination he appeared acutely ill and perspired profusely. The temperature was  $104.2^{\circ}\text{F.}$ ; the pulse-rate 120. There were scattered erythematous skin lesions on the left wrist, left shoulder, right side of the neck, chest, thighs, and feet (Plate 2, Fig. 3). Central pustules were seen in many lesions. There were diffuse reddish areas on the dorsum of the feet. Apart from a soft systolic murmur at the apex of the heart, the cardiac condition appeared normal. The second aortic sound was louder than the corresponding pulmonary sound. Both feet were moderately swollen, warm to touch, and tender, with pain referred to them on motion of the toes. The ankles were freely movable. The haemoglobin was 95 per cent. An electrocardiogram showed only left axis deviation. The diagnosis of gonococcal septicaemia was suggested.

The following day the eruption was more profuse, with definite predilection for distal parts of the limbs (Plate 2, Fig. 4). Particular attention was directed to the appearance of a haemorrhagic pustular lesion on the little finger of the right hand. At the site of injection of gonococcal vaccine (right thigh), there was now an indurated reddish area the size of a silver dollar. A small haemorrhage was found in the left lower conjunctiva. Examination of the fundi showed no abnormalities. A blood culture was taken and reported subsequently to contain gonococci in three flasks. The white-blood cell count was 30,000 with 86 per cent. polymorphonuclear leucocytes. The erythematous area on the right foot was interpreted as a tenosynovitis of gonococcal origin. The following morning the pustule situated on the little finger of the right hand assumed the form of a bulla with a haemorrhagic pustular centre. At this time the apical systolic murmur appeared to be more pronounced. Smear of a pustule revealed many pus cells but no organisms; culture of the contents was sterile. Many lesions were in the process of involution; the one on the dorsum of the left wrist had disappeared, leaving a small area of tender induration. The eruption underwent gradual and complete involution. The patient was treated by physiotherapy and intravenous typhoid vaccine. The temperature gradually fell to normal at the end of the second week and the sedimentation time was then two hours and ten minutes.

*Comment.* The past history, type of articular involvement, and the occurrence of tenosynovitis favoured the diagnosis of gonococcal infection. The features of the eruption appeared to substantiate the conception of benign gonococcal bacteraemia, despite the initial severity of illness and the auscultatory evidence of cardiac murmurs. The skin lesions showed definite favour for distal parts of limbs. The indurated erythematous area on the right thigh was theoretically interpreted as a possible equivalent of the Schwartzman phenomenon. Aside from the eruption, the only evidence of bacteraemia was the single positive blood culture, and its benignity was indicated by the transient course.<sup>2</sup>

#### *Discussion*

The cultivation of the gonococcus from the blood stream, joints, skin, and other structures and its isolation *post mortem* from vegetations in the heart constitute evidence that this organism invades the circulation. There are observers who believe that practically all instances of arthritis seen in gonococcal infections are caused by haematogenous invasion of the joints by this organism. The difficulties inherent in its cultivation and identification are well known. There are numerous examples where the use of even the most modern bacteriological methods may be fruitless, and in such cases the diagnosis must perforce be based on clinical grounds. The isolation of the gonococcus on one or several occasions merely indicates a bacteraemia but affords no precise information relative to the state of the heart or the prognosis. However, it appears that several consecutive positive cultures of blood are generally, but not necessarily, indicative of gonococcal endocarditis. Owing to difficulties in isolating the organism, an intermittent bacteraemia, as judged by bacteriological results, is inadequate evidence that the heart valves are unaffected.

It is probable that gonococci gain access to the general circulation through the superficial or deeper venous channels. The possibility of spread by lymphatics has been conjectured by some, denied by others. The incidence of bacteraemia in relation to the total number of cases of gonococcal infection is unknown and cannot be estimated accurately from statistical studies on post-mortem examinations, as recovery occurs in the vast majority of patients suffering from this type of blood stream invasion. Relative to the factors that operate either for fatality or for cure, there is little information at hand. It appears, however, that the presence of rheumatic heart disease may predispose to the engrafting of gonococcal endocarditis, but the precise mechanism is at present problematic. There is difference of opinion regarding the possibility of recovery in patients with gonococcal endo-

<sup>2</sup> Through the courtesy of Dr. A. M. Fishberg, I was able to observe an additional example of this syndrome, the features of which need no recital as they were analogous to those already described. The other cases were studied on the services of Dr. B. S. Oppenheimer and the late Dr. L. Kessel (The Mount Sinai Hospital). Thanks are due to Dr. William M. Hitzig for some of the observations and for helpful criticisms.

carditis; many observers believe that cures, if they do occur, are extremely rare. It is only fair to note that this complication was suspected in at least two of the five cases reported in this paper, but that subsequent observations appeared not to substantiate this view. There are statistical compilations on the incidence of recovery in gonococcal bacteraemia, the figures arrived at being based usually on the inclusion of cases with suspected (clinical) endocarditis as well as those without evidence of valvular disease. However, such general data must be utilized cautiously in support of the conception of cure in gonococcal endocarditis; it is essential to draw a sharp distinction between instances with valvular disease and those without. This differentiation is fundamental in evaluating the clinical significance of the syndrome described in this paper.

The evidence for gonococcal bacteraemia appeared to be unequivocal in four of the five cases cited in detail, the organism having been isolated from the blood, articulations, or skin lesions. In the remaining instance (Case 3) bacteriological proof was lacking, but the clinical course and the features of the eruption pointed to a systemic gonococcal infection. In general, the syndrome is characterized by the occurrence of fever, joint manifestations, and a special type of dermatosis. Corresponding to the age incidence of the disease, these cases are chiefly encountered in young adults of both sexes. The condition has a duration of from several days to a few months; in some instances a protracted course is attributable to a residual, slowly healing deforming arthritis, rather than to continuation of the bacteraemia. Critical analysis of the literature reveals a number of typical cases of a syndrome analogous to the one recorded in this paper (3, 10, 13, 15, 18, 20, 22). Probable instances have also been described by a few other observers (1, 9, 17, 21). As study of the condition tends to throw some light on the problem of gonococcal bacteraemia and on the pathogenesis of the skin lesions, it seems desirable to discuss the clinical features in detail. Familiarity with this syndrome appears to be useful, as in many instances careful questioning may fail to elicit a history of sexual exposure or of venereal infection, without which the practitioner will generally be loath to suspect or diagnose the condition.

1. *Local focus.* In many cases of gonococcal bacteraemia, the local focus from which dissemination takes place, may be active and acute; in other instances the primary process is clinically inactive and has *apparently* been healed for weeks, months, or even years. It is known that a urethral discharge may cease spontaneously with the onset of a severe febrile reaction, resuming flow when the temperature and constitutional symptoms have abated. The presence of a local focus is established more easily in males than in females; yet, in the syndrome under consideration the original gonorrhoeal focus was not found in the five cases reported in this paper and in the majority of instances described in the literature. Even when the gonococcus was isolated from sites of predilection, the mechanism by which it entered the circulation remained obscure. The factors of pregnancy and

menstruation as means of spreading the infection appeared to operate in some instances. Observers have noted that most cases have no demonstrable primary focus or that the process has been healed for varying intervals of time, but these observations must be regarded cautiously, as post-mortem examination has often shown that a supposedly cured gonorrhoeal infection may be still active and the probable locus for generalization of the disease. Similarly, gynaecological examinations may disclose no abnormalities; yet, an active gonorrhoeal focus may be present which is either clinically unrecognizable or is inaccessible to direct palpation. Pathological evidence seems to point to involvement of venous channels, notably the voluminous plexuses situated deeply about the prostate or adnexal structures. It is probable that the smaller venules may also be implicated. It is suggested, pending confirmation by pathological studies, that variations in severity of the clinical features may, perhaps, be due to differences in size of the feeding focus.

2. *Fever.* The temperature is usually remittent, but the irregularities are so marked that it is difficult to speak of a typical fever curve. There are no remarkable fluctuations of temperature such as are seen in the average example of gonococcal endocarditis. In many instances there is continued fever owing to the presence of an arthritic process rather than to a persistent bacteraemia.

3. *Joint affections.* As in other forms of gonococcal septicaemia, articular disease is a fairly constant feature, with but few exceptions. The type of joint manifestation cannot be differentiated from that observed in ordinary uncomplicated gonococcal arthritis. Frequently there is onset with polyarthritis, followed by localization in one or several joints. In many cases the condition is restricted *ab initio* to one of the favoured sites (knees, wrists, &c.). The physical findings may be limited to simple pain, with little attendant involvement of periarticular tissue; it is, however, more usual to find red, swollen, painful joints that, notably in the region of the wrist, give rise to characteristic periarticular swellings affecting adjacent parts. Gonococci are often demonstrable on aspiration of fluid from joints; this finding proves the haematogenous origin of the condition. Study of the recorded cases indicates that there is a definite tendency to spontaneous resolution. There are, however, instances in which residual deformities occur, and it is a question whether the therapeutic policy of immobilization and traction is a factor in the production of such sequelae. The value of vaccines and other forms of therapy cannot be assessed in view of the high incidence of spontaneous recovery. Puncture of joints is occasionally essential for diagnostic purposes, but repeated aspiration, when used for therapeutic purposes, appears to be a dubious, and in some instances a dangerous procedure. The occurrence of polyarthritis in gonococcal bacteraemia may produce a clinical picture resembling rheumatic fever; the analogy is closer when it is remembered that the onset is often with sore throat (Cases 2 and 3), (Schottmüller, 1921; Wheeler and Cornell, 1930).

4. *Skin lesions.* The morphological attributes of this dermatosis, considered in relation to the clinical picture, provide features that often lead the observer to diagnose correctly an illness otherwise obscure. The eruption is typically composed of a scanty number of lesions varying in number from one or two to six or eight in all; in occasional instances they may be distributed over the entire body (15, 19, 20). As a rule, the lesions are discrete; rarely does coalescence occur as an incidental event in the course of a profuse eruption (Massini, 1916). In typical cases the extremities are affected, with particular favour for their distal parts. Less commonly, isolated lesions are encountered on the trunk, face, scalp (Kerl, 1930), and oral mucous membranes (Case 1), (Cabot, 1927; Hodara *et al*, 1912), where, however, they appear to be less easily recognized. The tendency to occur in crops is a striking phenomenon. In the majority of cases there were, on the average, two additional outbreaks of lesions; in Case 3 the eruption was limited to but a single crop. This clinical feature substantiates the belief in the essential transiency of the bacteraemia. When numerous crops appear (Massini, 1916), this would seem to be evidence of continued invasion of the blood-stream by the gonococcus—an uncommon event in this syndrome. Generally the eruption arises during the febrile period, but rarely further development of lesions may be observed during intervals of apyrexia.

The primary element is an erythematous macule that speedily acquires a central 'vesicle' or pustule. In typical examples haemorrhage occurs in the centre of the lesion, and in many cases the exudation of fluid and cells causes bullous formation. The classical lesion in full development is a haemorrhagic purulent 'vesicle' or bulla, surrounded by a more or less broad erythematous areola. Occasionally there is noted an intermediary zone of relative pallor. Exudation may at times be so pronounced that rupture occurs, with the production of crusts, but I have not seen this secondary event lead to resemblances to keratoderma blenorrhagica. In any particular patient it is usual to encounter all phases of evolution, either because of the occurrence of additional fresh crops or because of the failure of individual lesions to develop beyond the erythematous, 'vesicular', or pustular stages. When the haemorrhagic component is lacking, the dermatosis becomes less easily recognized. In occasional instances isolated lesions may be painful or tender to touch, but there are usually no decided resemblances to the Osler nodes; the latter, for example, do not, as a rule, form vesicles or bullae or undergo suppuration. When the fingers or toes are sites of such tender lesions, the observer may consider the condition as *panaris* and resort to unnecessary surgery.

A smear of the contents of a lesion reveals numerous pus cells in various stages of disintegration. Organisms are only occasionally found on direct smear (Case 4); there are, however, a relatively large number of instances where positive results have been recorded (17, 18, 19, 20) and in some cases the organism was definitely identified by cultural methods. It is difficult

to isolate the gonococcus from the integument, but unsuccessful results are often related to the developmental stage of the cutaneous lesions, as the organism seems to enjoy but a brief existence in the skin. In Case 4 several pairs of intracellular Gram-negative diplococci were observed on direct smear, but a culture taken several days later revealed only a contaminating *Staphylococcus albus*. In Case 3 where direct examination failed to show any organisms, culture disclosed typical colonies of gonococci, the growth, however, being insufficient for agglutination tests. The presence of numerous pus cells in the absence of demonstrable micro-organisms is a combination of circumstances tending to cast suspicion on the gonococcus; for example, in other similar 'metastatic dermatoses' (*Streptococcus haemolyticus*, *Staphylococcus aureus*, *B. pyocyaneus*, &c.), there is usually no difficulty in isolating the causative agent. It is probable that the 'metastatic dermatosis' arises from the direct action of bacteria on skin, rather than the remote effect of toxins (Fraenkel, 1913 and 1920).

Histological studies of these skin lesions are few. In Kerl's case (1930) little information was gathered from microscopic examination. Wiedmann (1934) found necrosis of the vessel walls, to which he attributed the exudative phenomena in general and the haemorrhagic component in particular. Bacterial stains on skin sections are advocated for obscure cases of the disease; for example, I observed an instance of a related condition, chronic meningococcal septicaemia, in which the organism was found *in situ* in a biopsy specimen of skin, although several previous blood cultures had been sterile. It appears that this method of investigation has its greatest field of diagnostic usefulness in cases where the organism is difficult to isolate, but it will be generally necessary to study fresh or young efflorescences.

On the basis of Buschke's (1912) observations, the gonococcal eruptions are conveniently classified into four principal groups: (1) erythemas; (2) urticarial and nodose lesions; (3) haemorrhagic and bullous lesions; (4) hyperkeratosis. The cases forming the subject of this communication appear to fall into a subdivision of the third category. Review of the literature discloses another series of cases showing similar features, but distinguished by the occurrence of pure pustular lesions (DuBois, 1924; Dainow, 1927), the eruption being characterized by more widespread distribution, tendency to favour the trunk, comparative ease with which the gonococcus was isolated from fresh efflorescences, and, finally, evolution by crusting with the production of lesions resembling keratoderma blenorrhagica. Buschke (1912) and others have noted that there are numerous transitional examples. Despite this, there is, at present, no advantage to be gained from a revision of the classification.

#### *Differential Diagnosis of Skin Lesions*

(a) *Drug eruption.* Many dermatoses formerly attributed to gonococcal infection were probably due to the use of drugs (oil of sandalwood, copaiba, salicylates, urotropin, &c.). On the other hand, unrecognized gonococcal

eruptions are often considered as of drug origin. The occurrence of pustular lesions may be attributed to bromides (Filler, 1933) or to iodides (Rubenstone, 1932). In the cases described in this paper there was no evidence to incriminate a drug origin, 'balsamic' or otherwise.

(b) '*Erythema multiforme*'. Despite the many advances in morphological conception, the term 'erythema multiforme' still comprises a multiplicity of conditions. In another publication (Keil, 12) an attempt will be made to differentiate, on the basis of a clinico-dermatological correlation, at least six well-defined varieties of 'erythema multiforme', having certain features in common: (1) erythema multiforme exudativum (Hebra); (2) genuine rheumatic erythema multiforme; (3) erythema multiforme described by Osler; (4) the type of erythema multiforme representing a phase of 'systemic' lupus erythematosus; (5) the variety seen in chronic meningococcal septicaemia; and (6) the one described in this paper.

(c) *Haemorrhagic eruptions*. Conjunctival haemorrhages are occasionally encountered in the condition reported in this paper. These lesions are not especially common and seem to possess little importance as a diagnostic or prognostic sign; for example, their occurrence does not necessarily indicate a complicating bacterial endocarditis. The haemorrhagic vesiculo-pustular and bullous eruption is not to be confounded with various other types of generalized purpuric and petechial manifestations seen in occasional instances of gonococcal bacteraemia, with or without a complicating bacterial endocarditis. The haemorrhagic component in the dermatosis described in this paper is, in reality, a secondary element in a general exudative process (serum and blood cells), though it provides the distinguishing feature. The few platelet counts recorded show figures within the normal range.

Similar haemorrhagic bullae are observed in other forms of bacteraemia (*Streptococcus haemolyticus*, *Staphylococcus aureus*, and *B. pyocyaneus* among others). These may be differentiated by the concomitant manifestations; evolution of lesions, bacteriological findings (skin and blood culture), and the general clinical picture. Detailed exposition of these points would be beyond the scope of this article.

### *Prognosis*

Discounting a few other uncommon causes of death, the immediate prognosis in gonococcal septicaemia appears to depend on the presence or absence of superimposed endocarditis. This complication is uncommon as compared with the total number of cases of bacteraemia. The occurrence of gonococcal endocarditis generally signifies an impending fatality; in the absence of valvular disease, the prognosis *quoad vitam* may be regarded favourably in the vast majority of patients. There are a few recorded cases suggesting the possibility of complete healing of bacterial vegetations, but it appears likely that the conception has been largely formulated around clinical conjecture and a laudable desire to see cures in a fatal disease. Even if this possibility

is granted, its occurrence is probably extremely rare. In at least two of the five cases reported in this paper, gonococcal endocarditis was presumptively diagnosed, but the clinical course appeared not to substantiate this belief. Some observers have postulated the presence of a 'specific benign plastic endocarditis' (Faure-Beaulieu, 1906) from which recovery takes place, but this hypothesis lacks confirmation. The observation that patients exhibiting the haemorrhagic vesiculo-pustular and bullous type of eruption practically always get well weighs heavily against the opinion that gonococcal endocarditis was present in these cases. Even in the isolated example recorded by Massini (1916), where death occurred, endocardial disease was not found; the focus of dissemination was a purulent thrombosis of the periprosthetic plexus of veins. Massini's case appeared to differ in the unusual widespread distribution of skin lesions and the appearance of numerous crops indicating a persistent bacteraemia; death was caused by embolization of the right pulmonary artery and lobular pneumonia of the left lower lobe. Schottmüller (1921) discussing the question of cure in gonococcal endocarditis, cited two cases exhibiting the eruption described in this paper, the implication being that these patients had recovered from this complication. These observations are at variance with the view that the eruption is an expression of a condition characterized by sparing of the endocardium. The only case recorded in detail by Schottmüller had no evidence of endocarditis and, as was to be expected, recovery ensued. The occurrence of this haemorrhagic dermatosis cannot be used as evidence supporting the diagnosis of gonococcal endocarditis; the eruption appears not to arise from emboli derived from the valves of the heart. On the other hand, genuine cases of gonococcal endocarditis seem not to be accompanied by the foregoing type of eruption. It is not surprising, therefore, that endothelial cells (macrophages) were not found in smears of blood in the isolated instances in which such examination was made (Kerl, 1930).

It is interesting that in one case of this sort Klein (1933), utilizing the Schwartzman phenomenon, reported observations that seemed to indicate the presence of immune bodies to gonococcal exotoxin. He was unable to demonstrate complement-fixing, agglutinating, or precipitating antibodies, whereas clinical improvement appeared to parallel rise of titre in the 'anti-toxin of the Schwartzman category'. It is possible that the production of this 'new type of antibody' may be responsible for, or be concomitant with, the recovery that ensues; however, further investigation is essential for precise evaluation of this finding.

#### *Conclusions*

1. Five cases of gonococcal bacteraemia are described characterized by fever, articular disease, and a distinctive type of eruption.
2. The skin lesions are caused by haematogenous dissemination of the gonococcus, rather than by the indirect effect of toxæmia from a remote

focus. This probably also holds for other types of 'metastatic dermatoses' seen in the course of gonococcal infection.

3. A local focus is often not clinically demonstrable; failure to find it, therefore, does not eliminate the diagnosis of gonococcal bacteraemia.

4. Bacteraemia of this type is usually benign and complete recovery may be expected in the majority of instances.

5. One or several positive blood cultures need not necessarily indicate a complicating specific endocarditis.

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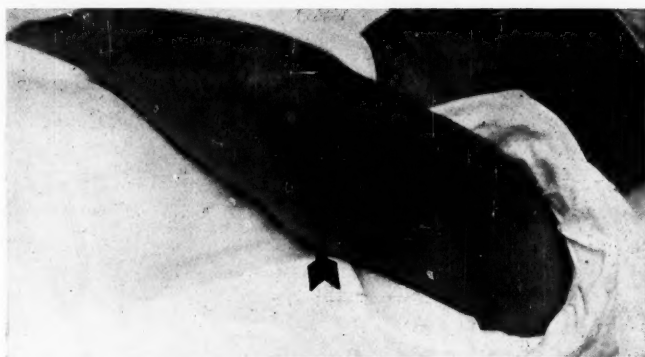


FIG. 1. Two erythematous crusted lesions about the left elbow (Case 4). Arrow points to lesion still showing the remains of a haemorrhagic bulla. The other spots shown in the photograph are ephelides



FIG. 2. Arrows point to the three scattered lesions on the lower limb (Case 4). The one over the ankle shows a haemorrhagic 'vesicle'

qua-te

Fig.



FIG. 3. Close-up of a typical 'vesicle' or pustule surrounded by an erythematous halo; the haemorrhagic component was in the stage of formation  
Lesion situated on the left thigh (Case 5)

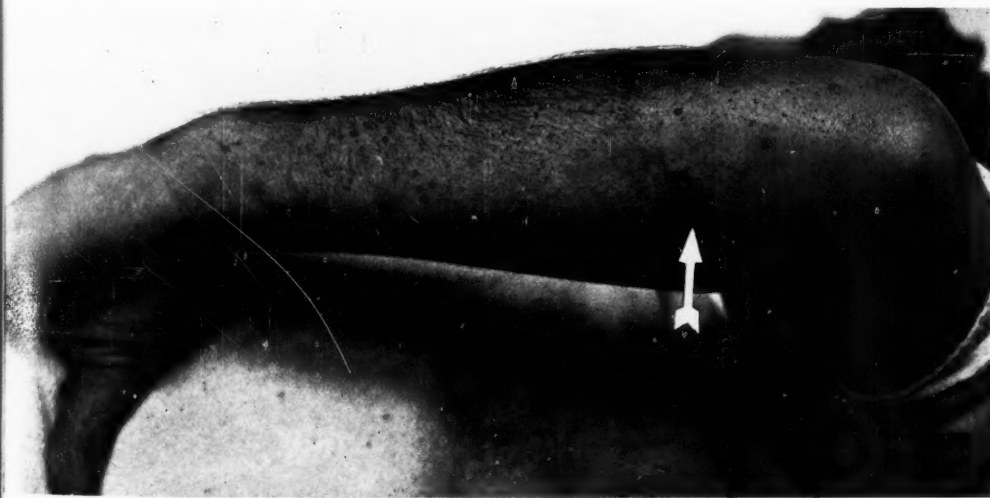


FIG. 4. Typical haemorrhagic pustule on the left forearm (Case 5). This was the only lesion on the photograph, the remainder being ephelides.

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## INSULIN RESISTANCE IN DIABETES MELLITUS AND THE EFFECT OF DIETARY CARBOHYDRATE<sup>1</sup>

BY O. L. V. DE WESSELOW AND W. J. GRIFFITHS

(From the Medical Unit Laboratories, St. Thomas's Hospital, London)

SINCE the earliest days of insulin therapy it has been recognized that cases of diabetes occur in which the injection of insulin produces a relatively small effect upon the blood-sugar. This so-called insulin resistance may be transitory, or may persist over long periods. The best-known instance of the former type is the increased resistance to insulin which accompanies infections, and which frequently leads to coma. In coma itself amounts of insulin are tolerated, and may be without effect upon the blood-sugar, far in excess of those required to stabilize the patient after his recovery. Various methods have been employed in the attempt to estimate the sensitivity of the diabetic to insulin, and are summarized by Falta (1936) in his recent monograph. They may be divided into two types: either the urinary sugar is determined and the amount of sugar metabolized per unit of injected insulin estimated—the so-called glucose equivalent—or an observation is made of the direct effect upon the blood-sugar of an intravenous or subcutaneous injection of insulin—the insulin-depression curve. In the latter a quantitative expression may be given to the result by determining the area of the depression.

Though at first sight the determination of insulin sensitivity by such methods may appear a simple matter, this is not actually the case. The constancy of the glucose equivalent may, for instance, be affected by variations in the production of endogenous insulin and carbohydrate, which cannot at present be allowed for, and since the method is based on the quantity of sugar excreted, alterations in the renal threshold come into consideration. The magnitude of the depression curve, on the other hand, is affected by the height of the initial blood-sugar, which is exceedingly variable in diabetics. Though it is assumed by many workers that insulin sensitivity can be measured by estimating the glucose equivalent, and by the study of the depression-curve, equally satisfactorily, we do not believe this to be the case, but incline to the opinion that the two methods of estimation are concerned with different metabolic functions. A factor of considerable importance in the determination of the glucose equivalent and one which is absent in the case of the insulin-depression effect, is the presence of the incoming sugar of the diet. In estimating the glucose

<sup>1</sup> Received August 13, 1937.

equivalent we are mainly concerned with the efficacy of insulin in enabling the tissues to deal with this influx of sugar; in the depression-curve, performed upon the fasting patient, with the ability of insulin to control the utilization and re-distribution of sugar already absorbed.

Himsworth (1936) in a recent paper entitled 'Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types' has studied the effect upon the blood-sugar of the diabetic of an intravenous injection of insulin followed immediately by the ingestion of glucose. While in some cases the blood-sugar remained at an approximately constant level, or even fell, in others a marked rise was seen: this latter group of patients were regarded as insulin-insensitive, the former as insulin-sensitive. He tentatively suggests that a general relationship exists between the type of response and the type of diabetic, the onset in the insulin-sensitive patients being as a rule acute, in the insulin-insensitive, insidious. The latter type is more common in, but not confined to, the elderly, and the sensitive cases are usually able to tolerate large increases in the carbohydrate of the diet without increase in the insulin dosage.

We ourselves have recently examined the effect of a previous injection of the serum of diabetic patients upon the fall in blood-sugar following intravenous injection of 0.2 unit of insulin in the rabbit (de Wesselow and Griffiths, 1936). We found that the sera of elderly and obese diabetics often modified the form of the depression-curve in the direction of a more early arrest in its fall and a more rapid return to the initial level of blood-sugar. The modification in the curve suggested a sensitization of the 'Gegenregulationseffekt', that is, the mechanism by which the fall in the blood-sugar is corrected by discharge of glucose from the liver. We suggested that in view of the work of Cope and Marks (1934), an excess of the anterior pituitary hormone which is believed to sensitize the liver to the glycogenolytic action of adrenaline might be present in the blood of certain diabetics. No effect upon the rabbit's insulin-depression curve followed the injection of normal sera, or the sera of the young diabetic, and we were led to the conclusion that in causation of certain cases of diabetes, but not of all, the anterior pituitary might play a part.

We were, therefore, naturally interested in Himsworth's (1936) observations as possibly offering a simpler and more rapid method of differentiating between different types of diabetes, and decided to test in this way an adequate number of cases, comparing the results with the clinical findings.

### *Experimental*

Our routine procedure has been to inject five units of Wellcome crystalline insulin intravenously into the fasting patient after making an initial blood-sugar determination, and to give the patient immediately 100 c.c. of 50 per cent. glucose solution by mouth. The blood-sugar was estimated again at 30 and 60 min. after the insulin injection, two estimations at these in-

tervals being, in our opinion, adequate for the determination of the difference in the response. There can be little doubt that a period of one hour ensures the necessary absorption of the ingested glucose, since by this time the blood-sugar curve in the normal has reached and usually passed its apex. The blood-sugar determinations were made upon 0.2 c.c. of capillary blood, obtained by a prick at the base of the thumb-nail, by MacLean's method.

Since we are dealing with only three blood-sugar determinations we have not attempted to measure the area enclosed in the blood-sugar curve, but have expressed our results as the algebraic sum of the differences between the initial blood-sugar and the values 30 and 60 min. after the insulin injection; thus with an initial blood-sugar of 100 mg. per 100 c.c., a blood-sugar at 30 min. of 90 mg. per 100 c.c., and at 60 min. of 140 mg. per 100 c.c., we should express the result as +30. Though we have expressed our results numerically, we have only done so for the sake of convenience. For reasons which will be apparent later, strict comparison between the curves is not possible, and our figures must be taken rather as an indication of the trend of the response than as being rigidly quantitative.

We have studied in all 62 diabetics by this method. Of these 21 were ward patients, examined in the morning fasting, and on a known diet (Group A); 14 were out-patients, examined in the morning fasting, and on a prescribed diet to which they may or may not have adhered (Group B); the remaining 27 were out-patients on a prescribed diet, who were examined in the afternoon six hours at least after their breakfast and morning insulin, when insulin was being taken, but who in a few cases had taken a small carbohydrate meal during this interval (Group C).

### Results

*The normal response.* Sixteen in-patients, 6 males and 10 females, varying in age from 17 to 58, showing no disorder of carbohydrate metabolism and receiving a full ward diet, were first tested in the morning after fasting for sixteen hours. The extent and duration of the response are shown in Fig. 1. The mean figures for the initial and subsequent blood-sugars were 0.089, 0.087, 0.109 mg. per 100 c.c. There is thus a slight tendency for the blood-sugar to fall during the first half-hour, and to rise above the initial figure at the hour: the response varied between the extremes of -17 to +70, with an average value of +18.

*The diabetic response.* The response of the various groups of diabetics (A, B, and C) are shown in Fig. 1. It will be seen that the spread in each group extends far beyond the limits of the normal, but that the general distribution of the response in the various groups is practically the same. From the distribution curve (Fig. 1) which includes all the diabetic responses, it is obvious that there is no suggestion of any sharp division between two types of insulin-sensitive and resistant, but that the extreme

instances of both conditions merge into a central group showing an approximately normal response.

Some diabetics are apparently more sensitive than the normals, but we doubt whether this actually represents their true condition. In normal patients, whose blood-sugar level at the beginning of the test is in the neighbourhood of 0.100 mg. per 100 c.c., a fall of 30 mg. to a hypoglycaemic

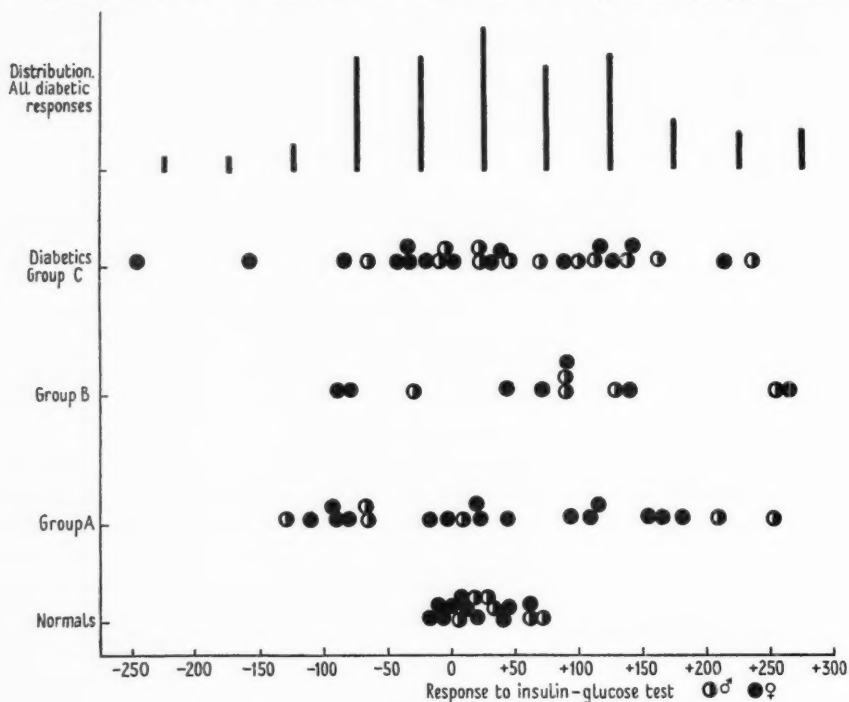


FIG. 1.

level will bring into action the regulating mechanism, and discharge of liver glycogen will occur and will raise the blood-sugar. The actual sensitivity will therefore be to some extent masked. In certain sensitive diabetics, in whom the blood-sugar is at a much higher level than the normal, a much greater fall would have to occur before the blood-sugar would reach a level at which this mechanism is evoked, even if we assume that it is normally active. For this reason it is to be expected that the effect of insulin on the blood-sugar in the sensitive diabetic will apparently often be greater than on that of the normal. Further, in cases of diabetes in which the initial blood-sugar is above the renal threshold, loss of sugar through the kidneys will tend to depress the blood-sugar curve and to diminish the apparent resistance. With these limitations the initial blood-sugar appears to be without effect upon the nature of the response (Fig. 2), in contradistinction to its well-known action on the insulin-depression curve.

If we assume that sensitivity and resistance to the insulin-glucose test are dependent upon the type of diabetes with which we are dealing, some correlation is to be expected between the type of response obtained and the clinical findings in the diabetic concerned. Himsworth (1936) believes that resistance is more frequently met with in the elderly diabetic in whom the disease has an insidious onset, sensitivity being as a rule characteristic of

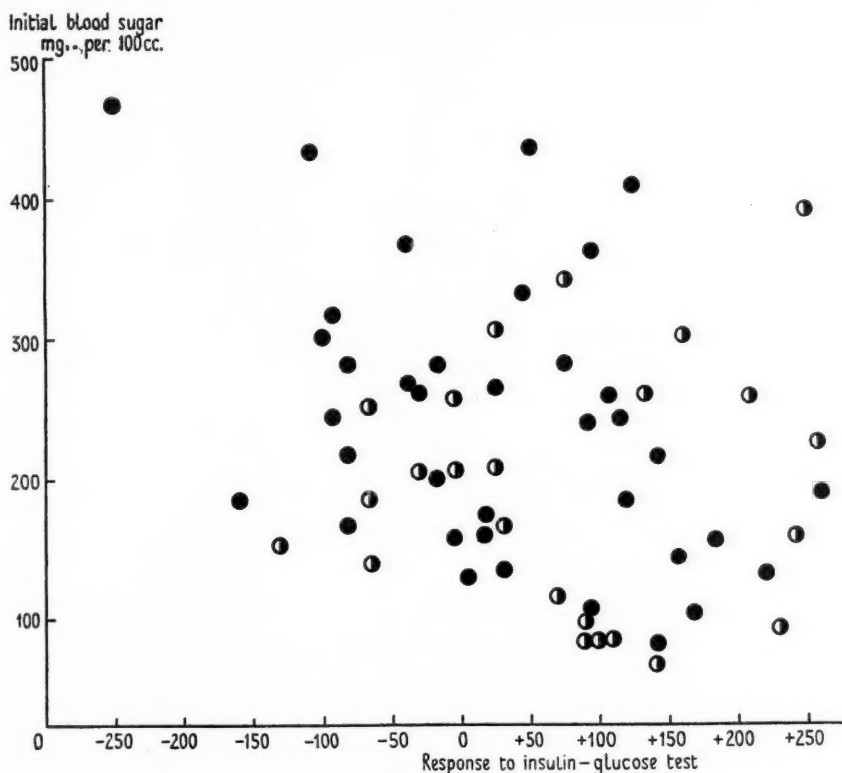


FIG. 2.

the young acute case. We have therefore reviewed our results in the light of age and the duration of the disease, and since we have always been interested in the existence of a type of diabetes in which the disease is accompanied by obesity and hypertension, and in which the general bodily condition is relatively little affected, we have also correlated our results with the blood-pressure findings, and with the body-weight.

That the sex of the patient is without effect upon the response will be apparent from Fig. 1. The relation of the response to blood-pressure is shown in Fig. 3. It is obvious that no correlation exists between the sensitivity or resistance to the test and the blood-pressure of the patient; this is also true for the age of the subject. Lastly, we have taken out a group of

diabetics who were very definitely over weight at the time of onset, and here again the type of response elicited is entirely variable (Table I).

Thus, we were unable to associate the form of the response to the test with any definite clinical features of our patients. Resistance may be encountered both in the young and in the elderly patients, in individuals of very different types of bodily build, in either sex, and irrespective of the

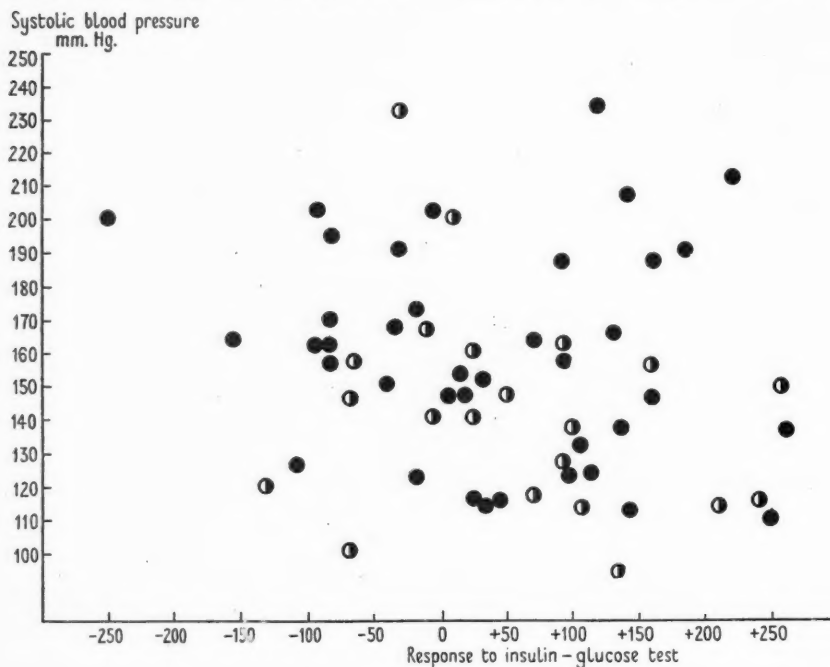


FIG. 3.

height of the blood-pressure. From the clinical aspect the test does not afford a means by which we can distinguish one particular type of diabetic from another.

It seemed possible, therefore, that the patient's resistance or sensitivity to the injected insulin might be significant rather of his general metabolic condition at the time of testing, than of any peculiarity of the type of diabetes from which he was suffering. If this were so, we should be able, by appropriate methods, to convert a diabetic from the insulin-resistant to the insulin-sensitive state, or vice versa. The most obvious way of accomplishing such a conversion would seem to be by dietetic means, in view of the known effects of the amount of carbohydrate ingested on the glucose tolerance in normals. Since in out-patients the actual diet taken cannot be controlled satisfactorily, we admitted six recent diabetics to the wards with the object of studying the effect on the response of stabilization on a relatively high carbohydrate diet with adequate insulin. As we expected,

in three of these a change in the response from pronounced resistance to sensitivity resulted; in two, the change though less marked was in the same direction, while in the sixth, after an initial fall in resistance, this again rose in association with the development of a boil and a marked ketonuria (Table II).

TABLE I

*Relation of Weight at Onset of Diabetes to Insulin glucose Response*

Sex.	Age at onset.	Present age.	Weight at onset, kg.	Height, cm;	Response to insulin-glucose test.
F	54	59	89	159	+78
F	73	73	93	165	-94
F	39	48	76	152	-28
F	54	56	83	159	-97
M	54	60	110	171	-28
F	62	65	86	165	+217
F	35	47	114	176	-81

TABLE II

*The Effect of Treatment on the Insulin-glucose Response in the Diabetic*

Case.	Treatment.	Blood-sugar figures after insulin-glucose, mg. per 100 c.c.	Response.
F.	100 gm. carbohydrate, insulin xii and xii, for 6 weeks	0.152; 0.218; 0.239	+153
	100 gm. carbohydrate, insulin xii and xii, for 7 weeks	0.135; 0.162; 0.222	+114
	200 gm. carbohydrate, insulin xvi and xvi, for 6 weeks	0.171; 0.171; 0.266	+95
McK.	Untreated	0.239; 0.268; 0.325	+115
	100 gm. carbohydrate, insulin xx and xx, 1 week	0.141; 0.218; 0.266	+202
	200 gm. carbohydrate, insulin xx and xx, 1 week	0.139; 0.179; 0.211	+112
	200 gm. carbohydrate, insulin xx and xx, 3 weeks	0.133; 0.122; 0.109	-35
M.	Untreated	0.271; 0.340; 0.330	+128
	100 gm. carbohydrate, insulin xxviii and xxviii, 2 weeks	0.211; 0.227; 0.264	+69
	200 gm. carbohydrate, insulin xxx and xxx, 8 days	0.129; 0.115; 0.137	-6
B.	Untreated	0.261; 0.352; 0.378	+208
	200 gm. carbohydrate, insulin x and x, 1 week	0.164; 0.241; 0.309	+222
	200 gm. carbohydrate, insulin xx and xx, 8 days	0.137; 0.133; 0.152	+11
W.	70 gm. carbohydrate, 3 days	0.159; 0.156; 0.179	+17
	200 gm. carbohydrate, insulin xii and xii, 2 weeks	0.131; 0.117; 0.115	-30
S.	Low carbohydrate diet, no insulin	0.271; 0.308; 0.340	+106
	200 gm. carbohydrate, insulin xxiv and xx, 8 days	0.171; 0.209; 0.211	+78
	200 gm. carbohydrate, insulin xx and xx, 3 weeks	0.177; 0.241; 0.286	+173*

\* Development of boil on face; ketosis.

It is interesting that resistance as evidenced by the insulin-glucose test may be met with in other conditions than diabetes, in which the carbohydrate metabolism is known to be deranged. Thus we have seen a high grade of resistance (+174) in a case of Cushing's syndrome, in which a high blood-sugar and glycosuria were present; and of seven cases of Graves' disease, two showed definitely enhanced resistance, while the response in the remainder was within normal limits. The two resistant cases were not to be distinguished clinically from the others; the resistance was not associated with a peculiarly high B.M.R., neither patient was emaciated, and both were taking a normal ward diet satisfactorily. After successful subtotal thyroidectomy insulin sensitivity was restored: in one case the B.M.R. was lowered from +41 to -20 per cent. and in the other from +39 to -3 per cent.: the alteration in the insulin-glucose response was from +118 to -32 in the former and from +165 to -9 in the latter.

### *Discussion*

Our first object in subjecting a series of diabetics of various degrees of severity to this method of examination was to determine whether it afforded a means by which diabetic patients could be separated into two types, based on a permanent and fundamental difference in their response to insulin, and showing a correlation with clinically dissimilar groups. Does this method of examination enable us to distinguish a group of diabetics characterized by persistent resistance to insulin, or are we merely dealing with a type of resistance of an unessential and transitory nature, such as we meet with in the infected diabetic, capable of modification by appropriate methods?

A study of the distribution curve does not suggest that the test actually affords a method of dividing diabetics into two groups: the curve shows a smooth transition from the sensitive to the resistant group without discontinuity. Any attempt to relate the type of response to certain known clinical features of the diabetic patient also meets with failure. Obesity, hypertension, age, sex, and duration of the disease cannot be correlated with the result of the test. That sensitivity is not confined to the treated patient is shown by the occurrence of normal sensitivity in at least four of our cases who were practically untreated. Lastly, in certain diabetics we have been able to transform resistance into sensitivity by diet and insulin treatment. For these reasons we regard the resistance to insulin which is shown by certain patients tested by this method as an expression of their metabolic condition at the time of examination.

This failure of the tissues to control the peripheral blood-sugar might be due to deficient storage or oxidation, or to both. We have no data on which to base an opinion on this point, but are more interested in the site of failure. One of us (Griffiths 1937), in an examination of the arterio-venous blood-sugar difference (*a-v* difference) in sensitive and resistant diabetics

during the insulin-glucose test, has found that the behaviour of the two types in this respect is essentially the same. In both the venous blood-sugar tends to exceed the arterial, and there is, therefore, a diminished peripheral utilization of sugar. A control of the technique employed showed that in normal subjects a marked *a-v* difference developed after the insulin and glucose, and in this respect the findings agree with those of other investigators. The rise in the arterial blood-sugar of the insulin-resistant patient cannot therefore be explained by a difference in the behaviour of his peripheral tissues as compared with those of the sensitive subject.

If variations in the reaction of the peripheral tissues do not account for the different responses in the two types we must seek an explanation of the resistance in a difference in the central action of insulin on the liver. The poor central response of the resistant group cannot be due to lack of insulin alone, since the same amount of insulin, when injected into the sensitive and normal subjects, is sufficient to control the blood-sugar. It seems, too, unlikely that the greater effectiveness of insulin in the sensitive group is due to augmentation of the injected insulin by secretion of endogenous insulin, since in many cases the blood-sugar during the test does not rise to a level which would stimulate such a secretion. We are therefore forced to the conclusion that in the resistant cases some factor is at work which diminishes the central action of insulin.

An explanation which suggests itself is the metabolic condition of the liver cell. The metabolic activity of the liver cell must to a large extent depend upon the diet. It is conceivable that on a carbohydrate-poor diet lack of capacity for storage develops; that the cell deficient in glycogen may anabolize incoming sugar indifferently; moreover, in conditions of carbohydrate scarcity, the gluconeogenic and glycogenolytic functions of the cell are called upon in order to cope with the drain of sugar from the blood to the tissues. In virtue of his lack of insulin, the liver cell of the diabetic resembles that of an individual upon a low-carbohydrate diet. As we have shown above, the resistant diabetic may become sensitive when placed on a high-carbohydrate ration adequately controlled by insulin. The shift from resistance to sensitivity would appear to depend on the adequacy of the carbohydrate in the diet, and the time during which a high-carbohydrate diet has been given, rather than upon the dosage of insulin, since in some cases the increased carbohydrate is tolerated, and sensitivity develops without increase in the insulin requirement. This suggestion is borne out by an analysis of 16 out-patients in whom the diabetic condition was adequately controlled as indicated by a satisfactory blood-sugar: of these, 10 were receiving 100 gm. of carbohydrate or less, with an average of 38 units of insulin, while six were receiving 120–200 gm. of carbohydrate with an average of 31 units of insulin; of the 10 cases on the low-carbohydrate ration, eight were resistant, while of the six cases on the high diet, four were sensitive. We may conclude that sensitivity to the test depends to a large extent on an adequate carbohydrate allowance in the diet; the

diabetic who is receiving such an allowance and who, with the help of extraneous insulin, is metabolizing a diet approximating to the normal, is likely to prove sensitive on examination by the insulin-glucose test.

It is tempting to correlate this finding with the Staub-Traugott phenomenon in the healthy subject. As is well-known, in the healthy subject the form and duration of the blood-sugar curve is conditioned by the composition of the diet: after a period on a low-carbohydrate diet, ingestion of glucose leads to a high and prolonged rise in the blood-sugar. We have studied the effect of such a diet upon the glucose-insulin test in the normal. Three individuals were tested before and after a 7-day period on a diet consisting of 6 gm. carbohydrate, 100 gm. protein, and 200 gm. of fat. Such a diet is, in our experience, calculated to modify considerably the blood-sugar curve, though it was obviously impossible to test this by direct experiment in these cases. The results obtained were equivocal: the mean of the three curves before was 0.099, 0.078, 0.119 mg. per 100 c.c.: after, 0.072, 0.091, 0.109 mg. per 100 c.c. In each case the tendency was towards an increased resistance, but the net result was unconvincing. The peripheral insulin action, as judged by the *a-v* difference, was normal and unchanged by the diet, as in the Staub-Traugott effect. We can only infer that the insulin-glucose test is a less sensitive method of demonstrating the altered activity of the liver cell than the Staub-Traugott method.<sup>2</sup>

Another condition in which depletion of liver glycogen is likely to occur is Graves' disease, since thyroxin is known to diminish the glycogen content of the liver in animals. Of seven cases of Graves' disease examined, all on a full diet (but starved for sixteen hours before the test), two were very definitely resistant, and one in addition was at the upper limit of the normal range. The occurrence of resistance could not be related to the increase in the B.M.R., or to the loss of body-weight of the patient. In two patients the resistance was transformed to sensitivity after successful sub-total thyroidectomy. It is interesting that in Graves' disease, as in diabetes, we observed the peripheral utilization of sugar to be absent or reduced; sensitivity to insulin, when present, is therefore attributable to the central mechanism. There is, of course, no method by which the actual content of glycogen in the liver can be determined in these patients, but it may be that extreme depletion of carbohydrate is present in the resistant cases, and produces a condition closely resembling that of the resistant diabetic.

Apart from the actual metabolic condition of the liver cell itself, it is possible that extraneous influences may affect the response to insulin and ingested glucose: of these, the most likely to be concerned would seem to be those anterior pituitary hormones which are known to induce in animals a resistance to insulin, and which act, at least in part, upon the liver cell.

<sup>2</sup> In none of these cases did any marked ketonuria appear. We have since seen a case on the same diet in which a high grade of insulin resistance, associated with a diminished peripheral utilization of sugar, developed coincidentally with the appearance of gross ketonuria (0.083, 0.131, 0.199 mg. per 100 c.c.).

Marks (1936) has suggested that on a low-carbohydrate diet the output of such hormones may be expected to increase. Such a mechanism would be paralleled by the effect of dehydration in increasing the secretion of the anti-diuretic body by the posterior lobe of the pituitary, as recently demonstrated by Gilman and Goodman (1937). If similar variations occur in the output of the hormones antagonistic to insulin, it is reasonable to suppose that their secretion might be increased in the diabetic on a low-carbohydrate diet, to fall again on stabilization on a high-carbohydrate ration.

The insulin-glucose test, while giving us a method by which we can determine the existing capacity of the diabetic to deal with ingested carbohydrate when supplied with insulin, does not enable us to divide our diabetics into two fundamentally distinct types. As far as we know there is at present no direct method by which this can be done, though we believe that such typing can be effected by the demonstration of a substance in the blood of certain diabetics which is capable of modifying the insulin-depression curve in the rabbit. Of the existence of such a substance in the sera of some elderly diabetics we have already produced evidence (de Wesselow and Griffiths, 1936), and have suggested that it resembles a pituitary hormone.

Card (1937) has examined the effect on the insulin-depression curve of high- and low-carbohydrate diets in the diabetic patient, selecting those patients who tolerated the high-carbohydrate diet without corresponding increase in insulin requirement. In spite of the considerable increase in the glucose-equivalent shown by these patients, no definite change was observed in the depression curve during the first 20 min. after the injection of insulin. It is evident that the insulin-depression curve gives no indication of the capacity of the diabetic to deal with incoming carbohydrate. On the other hand, as we have shown above, the high-carbohydrate diet definitely affects the response to the insulin-glucose test in these patients. Insulin 'sensitivity', therefore, can be only defined in terms of the particular test used; a subject sensitive by one method of examination not necessarily being sensitive by another. The insulin-depression curve and the insulin-glucose test are concerned with different metabolic functions: in the latter we are examining the capacity of the individual to deal with ingested glucose entering through the portal system; in the former, in the fasting patient in whom no absorption of carbohydrate from the gut is occurring, with the action of insulin as controlling the interchange of glucose between liver and tissues, and its utilization.

Whatever the cause of the variations in the response to the insulin-glucose test, the increase in sensitivity on the high-carbohydrate ration does at least afford an explanation of the ability shown by some diabetics to assimilate extra carbohydrate without increase in their insulin dosage (Ellis, 1934). The existence of resistance as demonstrated by this test is temporary, and its presence would seem to be an indication for increasing the carbohydrate allowance.

*Conclusions*

1. The responses of a group of clinically dissimilar diabetic patients to the insulin-glucose test of insulin sensitivity afford no evidence of the existence of two distinct types: instances of insulin sensitivity and resistance merge into a larger group showing an approximately normal response. The existence of apparent hypersensitivity to insulin in the diabetic is discussed.

2. The type of response is not related to the initial blood-sugar level, nor to the sex, age, blood-pressure, body-weight, or other definite clinical feature of the patients.

3. Resistance or sensitivity to injected insulin is shown to be determined by the general metabolic condition at the time of testing: it is possible, by means of carbohydrate and insulin, to convert a diabetic from the insulin-resistant to the insulin-sensitive state. That is to say, the more nearly the diet of the diabetic, and hence his metabolic processes approach, with the help of insulin, to the normal, the less likely is he to show resistance to insulin. This observation affords an explanation of the increased tolerance which is often acquired by the diabetic when the carbohydrate in his diet is increased.

4. The existence of insulin resistance in conditions other than diabetes in which carbohydrate metabolism is disturbed is noted, and suggestions regarding the possible cause of the phenomenon are advanced.

The work has been done by one of us, W. J. G., under the tenure of a Henry George Plimmer Fellowship.

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## OVER-STIMULATION OF THE VAGUS NERVE IN RHEUMATIC FEVER<sup>1</sup>

By J. D. KEITH

(From the Birmingham Children's Hospital)

### *Introduction*

THE high incidence of change in the auriculo-ventricular conduction in rheumatic fever has been recognized for many years. This alteration in the *P-R* interval is now accepted as one of the most characteristic abnormalities in the electrocardiogram of patients suffering from rheumatic heart disease; some observers have gone so far as to suggest that in young individuals excessive lengthening of the *P-R* interval is diagnostic of this disease provided syphilis is ruled out.

It was noticed that a number of children suffering from very mild rheumatic fever and chorea with little or no clinical signs of heart disease showed marked lengthening of the auriculo-ventricular conduction time in their electrocardiograms. This change appeared to occur in all forms of rheumatic fever and not infrequently bore little relationship to the severity of this disease. The four main manifestations of rheumatic infection, chorea, arthritis, nodules, and carditis occur singly or in various combinations. To link these manifestations together it seemed possible to use the auriculo-ventricular conduction time as a common denominator. To investigate this point a large number of cases has been reviewed and the details presented in this paper.

### *Auriculo-ventricular Conduction Time in Normal Children*

According to Seham (1924) the average auriculo-ventricular conduction time in normal children between the ages of 6 and 13 years is 0.138 sec. A similar figure (0.136 sec.) was obtained by Weiss (1931), whereas Shookhoff and Taran (1931), who compared 259 children between the ages of 6 and 15 years, found the normal average was 0.124 sec., they also found no marked alterations were present in diphtheria (heart-block excluded) and scarlet fever. Further, in 20 children they took daily electrocardiograms for two weeks and found no appreciable change. Summarized their actual averages were:

normals	0.124 sec.	scarlet fever	0.125 sec.
diphtheria	0.127 sec.	rheumatic fever	0.193 sec.

<sup>1</sup> Received September 8, 1937,

The most recent investigation on this question is that of Burnett and Taylor (1936), who examined 168 normal children between 1 and 8 years of age. They found the average *P-R* interval was 0.126 sec.

For the present study, electrocardiograms were taken on 26 children in this hospital who were convalescent from appendicitis, herniotomy, mastoiditis, &c. There was no evidence of heart disease on examination or in the history. The average *P-R* interval was 0.138 sec. with a range of 0.12 to 0.17 sec.

#### *Auriculo-ventricular Conduction in Children Suffering from Rheumatic Fever*

The auriculo-ventricular conduction time in children suffering from active rheumatic carditis has been studied by many investigators both in this country and abroad. Cohn and Swift (1924) found that 21.6 per cent. of 37 cases of rheumatic fever had *P-R* intervals of more than 0.21 sec. Swift (1925) found that 13.3 per cent. of 81 cases had *P-R* intervals of more than 0.21 sec. Reid and Kenway (1928) give 42.6 per cent. as the number of rheumatic carditis cases with conduction time over 0.21 sec. Shookhoff and Taran (1931) found an average of 0.193 sec. in a series of rheumatics with acute carditis. Cohn and Swift pointed out that inspiration produced a vagal effect on the conduction interval with slight lengthening, but this effect, and possible daily fluctuations, do not vary more than 0.02 sec. So they concluded that changes greater than this might be considered pathological. In their 37 cases of heart disease 84 per cent. had increased conduction time of more than 0.02 sec. Swift later (1925) put the figure at 86.5 per cent. and Reid and Kenway 92.3 per cent. Our study shows that there is little or no fluctuation found in normal children and patients suspected of being, but definitely proved not rheumatic, in the *P-R* interval on repeated electrocardiograms. Shookhoff and Taran found no physiological increase of the *P-R* with age during the period of 9 to 15 years and found instead rather a tendency to decrease, which makes any increase in the *P-R* interval more significant.

The following two case records indicate how the auriculo-ventricular conduction time may be lengthened in rheumatic patients who show very slight general reaction and little or no clinical evidence of carditis.

*Case 1.* O. Or., female, aged 10 years, was admitted in 1936 suffering from Sydenham's chorea. She had had a previous attack of chorea at 7 years of age with no resulting heart disease and had been well since. Two weeks before admission she developed nervous movements. On admission she appeared markedly choreic but no carditis was present. The relationship of the conduction time changes to the sedimentation rate, and clinical findings are summarized below. The *P-R* interval became progressively lengthened, but there was no change in the sedimentation rate and only a very faint systolic murmur developed, which disappeared ten days later. The chorea had subsided gradually until two months after admission her movements were normal and there was no evidence of carditis. The following is a summary of the figures:

Date.	P-R interval.	Rate.	Sedimentation rate.	Heart murmurs.
Admission	0.15 sec.	100	—	None
10 days	0.18 "	94	—	None
22 days	0.20 "	92	5 mm. p hr.	Very faint systolic murmur
1½ months	0.18 "	85	5 mm. p hr.	None
2 months	0.16 "	90	6 mm. p hr.	None
2½ months	0.15 "	90	—	None

*Case 2.* S. G., female, aged 3½ years, was admitted on 19.5.37 with rheumatic arthritis. She was well until the day before admission, when she refused to walk and complained of pain in the right knee, which was slightly swollen. On admission to hospital she appeared mildly ill, the temperature was 98, the pulse 120, and respiration 30. The right knee was somewhat swollen and tender. The heart was beating rapidly and the first sound was very soft, but no systolic murmur could be heard. The electrocardiogram showed a P-R interval of 0.18 sec. and low voltage in lead 3, the ST segment was slightly raised above the base line in leads 1 and 2. The next day the pain and swelling had almost completely subsided and movements were normal. The pulse-rate remained elevated at 110-120 for the first week and then fell to between 90 and 100. She appeared perfectly well after the first three or four days and the first heart sound gradually improved, but no systolic murmur occurred at any time. She was allowed up one month after admission, and seven weeks after the onset of the illness appeared perfectly normal in every respect. No abnormality could then be found in the heart by clinical examination or by electrocardiogram.

Date.	P-R interval.	Rate.	Comment.
21.5.37	0.18 sec.	120	Raised ST segment. Low voltage in lead 3
25.5.37	0.16 "	95	Raised ST segment. Low voltage in lead 3
31.5.37	0.15 "	100	Slightly raised ST segment. Low voltage in lead 3
2.7.37	0.12 "	125	ST segment normal. Good voltage. Nervous

These two cases illustrate a marked increase in the P-R interval occurring in rheumatic fever when there is a minimal cardiac lesion. In one case there was a transient systolic murmur and a normal sedimentation rate with an abnormally long conduction time. In the other no systolic murmur developed during the illness or following it, yet the characteristic changes occurred in the P-R interval.

In order to investigate the auriculo-ventricular conduction time in a large series of cases, it was decided to review the electrocardiograms of the children attending the rheumatic clinic. Most of these children had had rheumatic carditis, but a considerable number had normal hearts on clinical examination. During the past five years at this hospital frequent electrocardiograms have been taken on cases of rheumatic fever and chorea. On leaving the hospital the majority of these children go to a convalescent home for two months or longer, and certain of them are later admitted to a rheumatic school, where their activities can be supervised. These children attend the Rheumatic Clinic at the Children's Hospital at intervals of two weeks to six months, depending upon their condition. Over four hundred children are on the rheumatic clinic list, but we have included for this study only two hundred

who have been seen repeatedly during the last two years and who attend regularly. Electrocardiograms are usually taken at each visit, so that many have fifteen or more such records. The average number for each case is six, making a total of over twelve hundred electrocardiograms. These have been analysed in relation to disease manifestations and the clinical condition of the patient with particular reference to the conduction time. The maximum *P-R* interval and the minimum have been recorded in each case and the average results tabulated in four groups. (1) Those with rheumatic carditis. Many of these have had acute arthritis or milder joint pains but not chorea. In these cases the occurrence at any time of a systolic murmur has been taken as evidence of carditis. (2) Those with chorea and associated carditis. (3) Those with chorea alone and unaccompanied by carditis. The absence of a systolic murmur was taken as evidence that no carditis existed. (4) Those with arthritis and no clinical evidence of carditis.

CHART 1. *Variations in the P-R Intervals in 200 Cases of Rheumatic Fever and Chorea*

Group.	Cases.	Manifestations.	Average maximum <i>P-R</i> .	Average minimum <i>P-R</i> .	Difference.
1	86	Rheumatic carditis	0.177 sec.	0.137 sec.	0.040 sec.
2	59	Chorea and carditis	0.174 „	0.137 „	0.037 „
3	43	Chorea, no carditis	0.152 „	0.128 „	0.024 „
4	12	Arthritis, no carditis	0.160 „	0.127 „	0.033 „

In Chart 1 we see that the maximum *P-R* interval in each group is considerably greater than the normal average. As one might expect, the highest averages were in the first and second groups, i.e. those cases of rheumatic fever and chorea that developed carditis. There is not much to choose between these two groups, although the first is higher than the second. Also the range is greater in group 1 as is shown in Chart 2.

CHART 2. *Range of P-R Intervals*

Group.	Cases.	Manifestations.	Maximum <i>P-R</i> intervals.	Minimum <i>P-R</i> intervals.
1	86	Rheumatic carditis	0.28-0.15 sec.	0.20-0.12 sec.
2	59	Chorea and carditis	0.24-0.13 „	0.2-0.10 „
3	43	Chorea, no carditis	0.20-0.12 „	0.16-0.12 „
4	12	Arthritis, no carditis	0.17-0.14 „	0.15-0.12 „

It is interesting that groups 3 and 4, those with chorea and arthritis without heart disease, also show average *P-R* intervals greater than normal. This point can be emphasized again if the degree of alteration in conduction time for each case is studied. The difference between maximum and minimum *P-R* interval for each case is recorded and the percentage of cases showing an increase in the conduction time of more than 0.02 sec. has been tabulated. These figures are summarized in Chart 3. It will be seen that those with carditis showed the greatest increase, 80 and 81 per cent. These figures

compare closely with those reported by Cohn and Swift (1925) who found that 84 per cent. of cases of rheumatic heart disease showed transient alterations in the conduction time of more than 0.02 sec. Of particular significance are the figures for those that had no carditis. The chorea patients had 50 per cent. with *P-R* increases of more than 0.02 sec., and those with arthritis but without carditis 58 per cent.

CHART 3. *200 Cases of Rheumatic Fever and Chorea*

Group.	Cases.	Manifestations.	Percentages of cases in which the <i>P-R</i> interval increased more than 0.2 sec.
1	86	Carditis	80 per cent.
2	59	Chorea and carditis	81 „
3	43	Chorea, no carditis	50 „
4	12	Arthritis, no carditis	58 „

From these results it seems a fair deduction that the lengthening of the conduction time is the most constant and most characteristic feature of the disease as a whole. It links together all the various manifestations; thus it is a characteristic of choreic children without clinical heart disease as well as those with heart defect, although the degree of change is less in the former; it is a characteristic of children with rheumatic arthritis without cardiac involvement as well as those with a definite carditis.

These observations appeared to be of fundamental importance in the study of rheumatic fever and have led to an investigation of some of the theories offered to explain it. The widespread incidence of prolonged *P-R* intervals, even among the mildest cases, suggests a specific interference with the passage of the impulse from auricle to ventricle. It is well recognized that when the vagus nerve is stimulated the impulse passing from auricle to ventricle travels more slowly, and that it is delayed in varying degrees up to complete block depending upon the amount of stimulation employed.

#### *The Effect of Atropine on the P-R Interval in Rheumatic Heart Disease*

For this purpose 11 children suffering from acute rheumatic fever with *P-R* intervals of 0.19 sec. or over were chosen. All had moderately severe rheumatic carditis with apical systolic murmurs, and very soft or absent first heart sounds. Two children had mitral diastolic murmurs, in every instance the sedimentation rate had fallen to more normal levels at the time of investigation, the average being 18 mm. per hour (Landau's micro method). None had evidence of cardiac failure. The average age was 9 years and the atropine dosage was adjusted to the age of the child, the lowest being 1/100 grain for a 5-year-old boy and the highest 1/70 grain for a boy of 13 years. Ten children in the hospital convalescing from diseases other than rheumatic fever, who were almost completely well, and had normal hearts and no history of rheumatic fever, were used as controls. Electrocardiograms were taken before giving atropine and at 5 to 10 minute intervals after for from 35 to 45 minutes. All showed flushing of the face and some

degree of dryness of the mouth. The atropine was administered subcutaneously.

The first effects usually appeared 5 to 10 minutes later. An example is the following:—

J. B. aged 10 years.

Date.	Atropine.	Time.	Heart-rate.	P-R interval.
14.5.37	1/80 grain	Before atropine	79	0.20 sec.
		9 minutes after atropine	83	0.18 "
		16 " "	100	0.16 "
		21 " "	100	0.14 "
		35 " "	115	0.14 "

Most of the children had previously had electrocardiograms taken and showed no evidence of excitement at the beginning of the experiment. The *P-R* interval before atropine and the minimum after have been recorded along with the simultaneous changes in the heart-rate. These details have been set down in Charts 4 and 5. Chart 4 comprises the rheumatic group and indicates that the average *P-R* interval before atropine was 0.20 sec.

CHART 4. *Effect of Subcutaneous Injection of Atropine on the P-R Interval in Eleven Cases of Rheumatic Carditis*

No.	Initial.	Age.	Sedimentation rate mm. per hour.	Atropine dose in grains.	P-R interval in sec.			Heart-rate beats per min.		
					Before.	After.	Diff.	Before.	After.	Diff.
1	O. O.	10	10	1/75	0.20	0.14	0.06	88	125	37
2	A. J.	9	30	1/75	0.20	0.16	0.04	110	115	5
3	M. F.	7	—	1/80	0.20	0.13	0.07	100	150	50
4	V. F.	10	12	1/80	0.20	0.14	0.06	93	107	14
5	H. R.	13	23	1/70	0.21	0.16	0.05	65	125	60
6	A. W.	11	10	1/75	0.20	0.16	0.04	75	100	25
7	J. B.	10	10	1/80	0.20	0.14	0.06	79	100	21
8	G. T.	12	12	1/75	0.19	0.16	0.03	79	85	6
9	G. G.	5	—	1/100	0.20	0.16	0.04	83	125	42
10	D. H.	6	28	1/92	0.20	0.16	0.04	100	125	25
11	D. P.	7	25	1/85	0.20	0.16	0.04	88	115	27
Averages					0.20	0.152	0.048	87	115	28

(0.19 to 0.21 sec.) and the average minimum after atropine was 0.152 sec. (0.13 to 0.16 sec.). There was then an average reduction in the conduction time after atropine of 0.048 sec. The average heart-rate before was 87 beats per minute, and after 115, with an average alteration of 28. The effect of atropine on heart-rate varied considerably from case to case. The maximum increase in rate was 60 and the minimum 5 beats per minute, yet the changes in the *P-R* interval were of the same order throughout, showing a relatively constant reduction. From this it appears that atropine has a direct effect on the conduction system in these cases, but there is also an indirect effect due to the increase in heart-rate which is difficult to dissociate.

Chart 5 records the average *P-R* intervals of the control cases before and after atropine. The average before was 0.143 sec. (0.12 to 0.16 sec.) and after it was 0.13 sec. (0.12 to 0.15 sec.). This gives an average reduction of the *P-R* interval in the whole group of 0.013 sec. which is very much less

than that found in the rheumatic fever group. The heart-rate showed an increase averaging 30 beats per minute, which corresponds closely with the rheumatic group of 28. This would tend to minimize the importance of the rate change in reducing the *P-R* interval and stress the direct action of the atropine on the conduction system. These results coincide closely with those of Bruenn (1937) who found the average reduction in *P-R* in the patients with normal hearts to be 0.014 sec. The atropine in his cases was given intravenously. In his group of rheumatic fever patients the average conduction time was longer in this group (0.245 sec. as compared with 0.20 sec.). The average reduction was correspondingly greater, being 0.07 sec. as compared with our 0.048 sec. However, the two series are essentially in agreement in these respects. None of the cases of rheumatic carditis were

CHART 5. *Effect of Subcutaneous Injection of Atropine on Convalescent Patients (not Rheumatic) with no Heart Disease*

No.	Initial.	Age.	Atropine dose in grains.	<i>P-R</i> interval in sec.			Heart-rate beats per min.		
				Before.	After.	Diff.	Before.	After.	Diff.
1	P. T.	8	1/85	0.16	0.12	0.04	100	150	50
2	A. T.	9	1/80	0.16	0.15	0.01	93	136	43
3	K. P.	11	1/75	0.16	0.14	0.02	90	107	17
4	D. Sa.	6	1/100	0.14	0.11	0.03	100	105	5
5	D. Sc.	12	1/80	0.14	0.14	0.00	100	130	30
6	C. M.	10	1/75	0.14	0.14	0.00	110	120	10
7	L. T.	4	1/100	0.13	0.13	0.00	100	150	50
8	L. C.	9	1/80	0.14	0.12	0.02	100	125	25
9	J. P.	11	1/75	0.14	0.13	0.01	93	124	31
10	W. M.	7	1/85	0.12	0.12	0.00	82	130	48
Averages				0.143	0.13	0.013	97	127	30

very far advanced in the disease, most of them being in their first attack. Although two had diastolic murmurs in the mitral area, none had mitral stenosis. This probably accounts for the fact that all responded to atropine with shortening of the *P-R* interval, whereas Bruenn found two advanced cases that showed no change to atropine injections.

#### *Effect of Adrenaline on the P-R Interval in Rheumatic Heart Disease*

Similar experiments were carried out on six of the cases of rheumatic fever. It was considered desirable that the heart-rate of this group should be the same as the other two groups, but it was found, however, that relatively large doses of adrenaline (see Chart 6) had to be administered in order to produce a comparable increase in heart-rate.

The average conduction time before the administration was 0.19 sec. and after was 0.163 sec. The change in rate was not as great on the average as after atropine, but it was felt advisable not to give any larger doses. However, the increase in rate was 23 beats per minute, which is something of the same order as with atropine, which was 28. The average decrease in the *P-R* interval in these cases of rheumatic fever after adrenaline was 0.027

sec., which is not as great as that produced by atropine in the rheumatic, but is greater than that produced by atropine in the control children.

In his recent communication Bruenn (1937) reports the effect of adrenaline on rheumatic fever patients with prolonged conduction times. He administered the adrenaline in two doses twenty minutes apart. Following one dose the increase in rate averaged 11.2 beats per minute. The *P-R* interval change

CHART 6. *Effect of Subcutaneous Administration of Adrenaline (1:1000) on the P-R Interval in Six Cases of Rheumatic Carditis*

No.	Initial.	Age.	Sedimentation rate mm. per hour.	Adrenaline dose in minims 1:1000.	P-R interval in sec.			Heart-rate beats per min.		
					Before.	After.	Diff.	Before.	After.	Diff.
1	O. O.	10	8	17	0.18	0.16	0.02	100	122	22
2	A. J.	9	25	17	0.20	0.16	0.04	110	125	15
3	M. F.	7	—	15	0.18	0.16	0.02	100	125	25
4	V. F.	10	12	16	0.20	0.16	0.04	100	124	24
5	H. R.	13	23	20	0.20	0.16	0.04	83	107	24
6	A. W.	11	10	21	0.18	0.18	0.00	65	93	28
Averages					0.19	0.163	0.027	93	127	23

was practically identical with his controls, being 0.018 sec. in the rheumatic groups and 0.02 sec. in the control group. After a second dose only two cases in the rheumatic group showed a decrease in the *P-R* interval. In the three remaining cases the *P-R* was increased. In two there was a transient heart-block and in all cases numerous premature beats were observed both nodal and ventricular in origin. These effects were temporary and the electrocardiograms returned to normal within twenty minutes after the second injection of adrenaline. None of these abnormalities of rhythm were observed following the administration of adrenaline, but similar transient effects were found after atropine. One child developed frequent ventricular extra systoles which disappeared twenty minutes after the injection of the atropine when the heart-rate had increased from 60 to 75 beats per minute. Another child had a *P-R* interval of 0.20 sec. before the atropine injection, twelve minutes after 15 minims of atropine the *P-R* interval had increased to 0.30 sec. This very long conduction time then rapidly shortened to 0.14 sec. 31 min. after the injection. Bruenn concluded from his observations that the conduction defect in rheumatic fever is due in part at least to an increase in vagal tone. The changes in rate and rhythm of the heart after the second dose of adrenaline he suggests are due to a rise in blood pressure with a resultant secondary stimulation of the vagal centres. These changes did not occur in controls, therefore he suggests that in rheumatic fever the focus of vagal irritation is in the medulla, which is rendered hypersensitive by the rheumatic toxins. An alternative explanation appears possible in the experiments performed by Bruenn. Adrenaline soon depletes the carbohydrate stores in the heart, and a second dose in the presence of a damaged heart may be sufficient to produce the alterations in rhythm and conduction reported. Similar abnormalities have been recorded in hypoglycaemia after insulin administration. From the results recorded in this paper it would

appear likely that during the very acute stages of rheumatic carditis the greatly increased heart-rate may, to some extent, mask the mechanism which is lengthening the conduction time. As the more acute process subsides the *P-R* interval which may have been moderately prolonged becomes more so, at the same time the heart-rate may fall to normal or even a subnormal level for a while. These latter changes may occur while the sedimentation rate remains above normal, that is to say during the continuance of the active process. The lengthening of the *P-R* interval in rheumatic fever has been presented as the chief evidence of over-stimulation of the vagus. Certain other supporting evidence of a less definite nature is at hand, and this is discussed under two headings: (1) pulse-rate, (2) abdominal pain and vomiting.

#### *Pulse-rate*

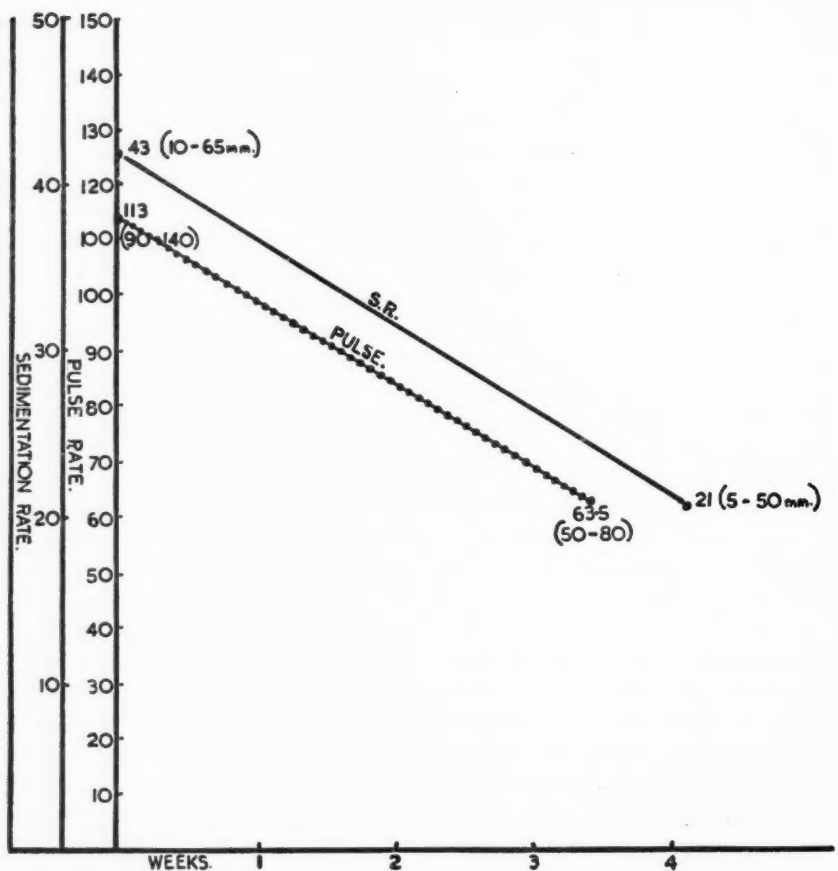
An increased pulse-rate is characteristic of acutely active rheumatic fever. When the more acute process of the disease subsides, the pulse may return to normal, subnormal, or remain persistently elevated. A persistently high pulse-rate is usually associated with marked damage in the myocardium and endocardium, frequently the result of more than one attack of rheumatism. Exceedingly mild damage to the myocardium sometimes occurs in chorea where a systolic murmur may develop while the sedimentation rate remains normal. In these cases the pulse-rate shows no abnormal increase throughout the stay in hospital and only varies as a normal pulse would. Some children were observed to have a heart-rate slower than normal as the infection subsided, although there was still some evidence of activity. These were noticed to occur mainly in the first attack of rheumatic fever and to comprise a group that was of a moderately severe type, neither very mild nor very severe. Thirty children have been selected that fall into this group. They were all instances of rheumatic fever in their first attack of heart disease, the onset being in each case within two weeks prior to admission to hospital. The sedimentation rate and pulse were recorded on admission, and the slowest pulse-rate noted during the first four weeks in hospital. These details are shown in Chart 7.

The average pulse on admission was 113 beats per minute and the average lowest during the first four weeks was 63.5 beats per minute. This is below normal for the average age in the group which was 8-9 years. Vierordt in a study of 934 normal children recorded the variations in pulse-rate at different ages. The average maximum frequency between 8 and 9 years was 88.8 beats per minute, and the average minimum frequency between 8 and 9 years was 72 beats per minute. The minimum frequency is definitely higher than the average of the lowest pulse-rates in this series of 30 rheumatic children. Yet at the same time the sedimentation rate was still elevated (see Chart 7). Therefore it is pointed out that with all the evidence of activity the pulse-rate remained subnormal. Further, it has been found that the bradycardia can be released by the administration of atropine. This slowing of the pulse

is not presented as characteristic of rheumatic fever, for it may occur after any infection, but these details are of interest in association with the more characteristic evidence of over-activity of the vagus recorded in the first

CHART 7.

PULSE-RATE IN 30 CASES OF ACTIVE RHEUMATIC HEART-DISEASE IN THEIR FIRST ATTACK.



AVERAGE P.R. INTERVAL = 0.186 SECS. RANGE = 0.12 - 0.25 SECS.  
 AVERAGE AGE = 8.7 YRS. RANGE = 4 - 12 YRS.

part of this communication. It may be significant that this bradycardia occurs in rheumatic fever while there are so many signs of continued activity, and it is worth pointing out that bradycardia is found more frequently after

some diseases than others, being more common after scarlet fever than diphtheria.

### *Abdominal Pain and Vomiting*

Abdominal pain and vomiting are not uncommon in children with rheumatic fever. These symptoms occur most frequently in the younger patients, and often at the onset of the attack. Frequently they are met with in the severe or advanced cases where there is pericarditis, pleurisy, or cardiac failure, but many cases of acute rheumatic fever that exhibit abdominal pain and vomiting do not have evidence of these conditions. Young children in their first attack not uncommonly have these symptoms, and it seems likely that the cause is substantially different. One such child had repeated attacks of abdominal pain and vomiting, and occasionally the pain was followed by a slightly loose bowel motion. These findings were associated with a lengthened conduction time and a systolic murmur. The suggestion is offered that in some instances the occurrence of abdominal pain and vomiting in the early stages of rheumatic fever where there is no evidence of pericarditis is due to an over-stimulation of the vagal nerve supply to the gastro-intestinal tract.

### *Comment*

These observations provide new evidence for discussing the various theories advanced regarding the cause of the conduction time alterations in rheumatic fever. The most widely accepted theory is that designating certain local pathological changes as the cause of conduction time changes. The pathological changes in the region of the auricular-ventricular node have been studied with great care by Gross and Freid. They found changes characteristic of rheumatic fever in the small arteries and a variety of inflammatory and vascular phenomena including cellular infiltration of the node and surrounding tissues, oedema, and destruction of collagen. They concluded that exudative or vascular change is evident in the node and bundle tissues in approximately 66 per cent. of active cases. To account for these very localized pathological changes in rheumatic fever and their relation to the conduction time they suggest two possibilities: (a) a spread of the disease process from the root of the aorta where Gross has shown that pathological changes are frequently present in rheumatic fever, (b) a compression of cells in the bundle tissue by oedema where it is surrounded by the rigid structure of the septum. This explanation is perhaps applicable to the cases of Gross and Freid where the study has been made on severe cases that died of the disease, but it does not furnish a satisfactory explanation of the marked increase in conduction time in the very mild cases referred to in this study, in which there is no evidence of aortic lesions and in which oedema of the bundle of His is unlikely to be present. The same criticism may be applied to the

theory that the lengthened conduction time is due to the action of toxins. If toxins are present in these very mild cases they must be specific for the conduction system of the heart and be so attenuated as to produce little or no general reaction. It may be that the mechanism controlling the conduction time, in the hearts of children at the age rheumatic fever develops, is unusually sensitive and responds to very mild toxins. Again, it is possible that this mechanism may at times become unbalanced even without the presence of toxins and result in a prolonged conduction time. It seems probable from this study that the essential feature of this mechanism in rheumatic fever is an over-stimulation of the vagus. The origin of this over-activity is obscure, but the evidence presented points to a peripheral abnormality, since it has been shown that the conduction time changes may occur without a generalized reaction, also they often persist for weeks or months after the acute infection has subsided and evidence of a generalized process has disappeared. The pathological evidence of disease in these children is mainly in the heart, and there is little to show in other parts of the body. For these reasons it seems more likely that the site of over-stimulation of the vagus lies in its terminations in the heart rather than in the medulla. Furthermore, it may be significant that the sites of the most abundant vagal nerve supply in the heart are the places where one finds such a high incidence of pathological change in rheumatic fever, the left auricle, the pulmonary and aortic roots, the arteries, and the auriculo-ventricular node.

According to current physiological observations, when the vagus is stimulated its effect is produced by the release of acetylcholine at its ganglia in the heart and at the terminations of the post-ganglionic fibres in the specialized neuro-muscular system and in the coronary arteries. The effect of acetylcholine on the heart has been investigated by Hall (1936), who gave dogs repeated injections intravenously and *post mortem* all but two of these dogs showed heart damage with areas of hyalinization and fibrosis in the muscle and hyaline degeneration and fibrosis of the medium and small coronary arteries. Several kinds of dysfunction of this chemical impulse conducting mechanism would appear possible to produce the abnormalities discussed in this paper. One should consider excess sensitivity of the muscle, or an excess liberation of acetylcholine, an interference with the process of destruction of acetylcholine or a potentiation of its action when liberated.

### *Summary*

Evidence has been presented of over-stimulation of the vagus in acute rheumatic fever in children. The mechanism of this has been discussed, and it is suggested that it is the result of direct over-activity of the parasympathetic nerve endings in the heart. The relationship of these observations to the pathological processes of the disease are briefly referred to. Further investigation is being conducted along these lines.

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SOME RARE TYPES OF MACROCYTIC ANAEMIA<sup>1</sup>

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*Introduction*

THE characteristic picture of the erythrocytes in the relapse stage of pernicious anaemia may be summarized as follows: macrocytosis, hyperchromia, and a marked degree of anisocytosis which is particularly well depicted by the shift to the right and the wide base of the Price-Jones curve. The feature of the pathologist's report on blood sent for examination, on which the great majority of doctors rely for the diagnosis of pernicious anaemia, is a colour index over unity. It is one of the objects of this communication to stress the fact that cases of severe macrocytic anaemia with colour indices over unity, which are not cases of pernicious anaemia, occur not infrequently.

The work of Castle (1929, 1930, 1931) has clarified our conception of the aetiology of the macrocytic anaemias due to lack of the anti-pernicious anaemia factor. Included in this group are Addisonian pernicious anaemia, which results from a failure of production of the intrinsic factor, the tropical macrocytic anaemia of Indian women, due to deficiency of extrinsic factor, and a group of diseases in which failure of absorption of the anti-pernicious anaemia factor occurs, as in tropical and non-tropical sprue and certain other pathological conditions of the gastro-intestinal tract. Failure in production or absorption of the anti-anaemic factor is by far the most common cause of a macrocytic anaemia. Nevertheless cases of severe macrocytic anaemia occur which are not connected with deficiency of the anti-anaemic factor, and which may arise in diseases widely differing one from the other. Lastly, there is a group of macrocytic anaemias which appear to be a connecting link between the above groups, namely, the macrocytic anaemias occurring in severe disease of the liver. Whether liver disease produces this effect by a failure in the storage mechanism, by a failure in the final stage of the synthesis of the anti-anaemic factor, or by some toxic effect of abnormal metabolic products on the bone-marrow, is a problem which will be discussed in this paper.

There are at least three good reasons which justify the publication of clinical, haematological, and pathological data obtained from the study of cases of severe macrocytic anaemia that are not due to a failure in the production or absorption of the anti-anaemic factor. Firstly, their recognition is demanded by the very serious prognosis. Secondly, their failure to

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respond to liver therapy may lead to dissatisfaction with a product which is highly successful in the right type of case. Thirdly, the treatment prescribed must vary according to the type of macrocytic anaemia diagnosed. Thus in the group of macrocytic haemolytic anaemias, splenectomy, and not liver extract therapy, offers the only chance of a successful outcome, and a fatal result may occur from a haemolytic crisis if the correct diagnosis is not made in time. It is essential to realize that any case of anaemia with a high colour index which fails to respond to adequate amounts of a reliable liver extract, should be referred to an expert haematologist for special investigation.

The rarity of these types of macrocytic anaemia and our ignorance of their aetiology and pathology make it eminently desirable that when such a case is seen it should be investigated fully. In addition to the employment of recognized clinical, biochemical, and haematological methods, we would draw attention to the need of studying by special means the bone-marrow and the reticulo-endothelial system; and this requires a special training over a long period. Before this obscure group of anaemias can be properly classified and elucidated, a large number of cases which have been fully investigated must be collected. For this purpose co-operation between various centres interested in haematology is necessary. Material obtained by biopsy or at autopsy should be specially studied at one centre where a research worker devoting himself to this problem would be installed.

In a previous issue of this Journal one of us has reported nine cases of macrocytic haemolytic anaemia (Davidson, 1932). In three of these the condition was due to Hodgkin's disease; in another three the diagnosis was 'acquired haemolytic jaundice'; in one the haemolytic process was due to lead poisoning; while in two cases no adequate explanation of the excessive blood destruction was found. In this communication we report 12 additional cases of rare forms of macrocytic anaemia which we have divided into four groups as follows:

*Group I.* Cases of microcytic hypochromic anaemia which developed a macrocytic anaemia, one of which failed to respond to all forms of treatment.

*Group II.* Cases of macrocytic anaemia associated with disease of the liver.

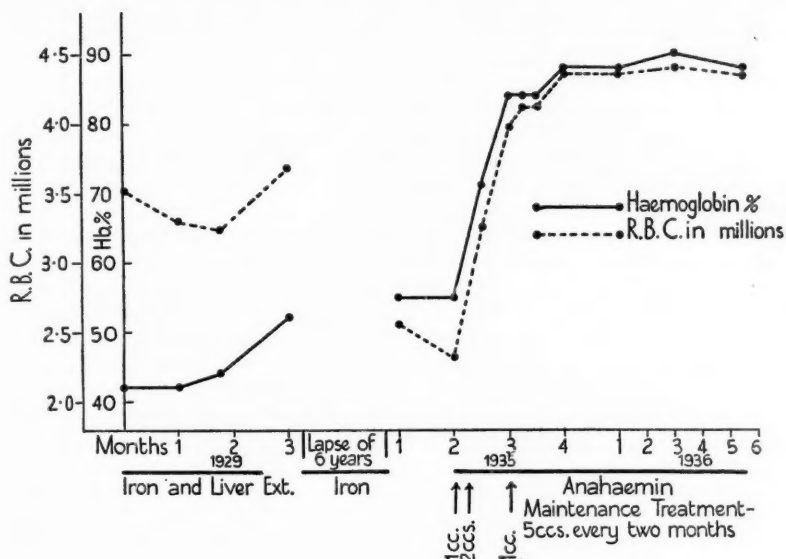
*Group III.* Macrocytic haemolytic anaemias, including a case of reticulo-endotheliosis, and a case of haemolytic anaemia due to *Salmonella* infection.

*Group IV.* A miscellaneous group of cases of macrocytic anaemia in which the primary fault appears to be in the bone-marrow: aplastic anaemia, (?) achrestic anaemia, and aleukaemic lymphoblastosis.

*Case 1.* Mrs. H. B., aged 55. Admitted to Aberdeen Royal Infirmary under one of us (L. S. P. D.) on 23.7.35, complaining of weakness and loss of appetite.

*History of previous health.* The patient gave a long history of disability.

Since the age of 40, when she was operated on for appendicular abscess, she has been weak and easily tired, but not sufficiently so to make her consult her doctor. For twelve years she has had difficulty in swallowing solid foods, particularly red meat. Her tongue has frequently been sore. In 1929 she developed haemorrhage from piles, and the weakness increased. At the same time she began to have attacks of severe pain in the right



CASE 1.

upper abdomen, and was admitted to the wards of Dr. Thomas Fraser in Aberdeen Royal Infirmary. Examination of the notes made at this time showed the following relevant details: the thyroid gland was moderately enlarged, soft, and freely movable; there was no evidence of toxicity. The spleen was enlarged; the edge was just palpable at the costal margin. A fractional test meal revealed achlorhydria with low combined acidity; histamine was not given. Barium meal showed nothing abnormal. Visualization of the gall-bladder by the oral method was unsuccessful. Blood examinations made at intervals were as follows:

Date.	Hb. %.	R.B.C. Millions.	C.I.	W.B.C.
21.7.29	42	3.53	0.59	5,400
31.8.29	42	3.30	0.64	5,400
17.9.29	45	3.23	0.70	4,625
5.11.29	52	3.73	0.70	4,375

The report of the late Dr. G. M. Duncan, Pathologist to Aberdeen Royal Infirmary, on films made on 21.7.29, was:

'Well-marked central pallor of staining, poikilocytosis and anisocytosis. No megalocytosis. No nucleated red-blood cells. Differential white count normal'.

The haemorrhoids were treated surgically and the patient gradually

regained strength. Another severe attack of abdominal pain, on this occasion associated with jaundice, occurred in 1932. She was again admitted to Aberdeen Royal Infirmary, and on 13th October, 1932, cholecystectomy was performed by Mr. G. H. Colt. Several gall-stones were present.

In 1933 the patient developed a blood-stained vaginal discharge (seven years after the occurrence of the menopause). Occasionally considerable amounts of frank blood were lost. A clinical diagnosis of carcinoma of the cervix uteri was made, but on section a non-malignant type of growth of the cervix was found. Radium was inserted. Since then there has been no recurrence of the discharge.

*History of present illness.* In April 1935 the patient fell downstairs and bruised her back so severely that she had to stay in bed for several days. She is emphatic that since this time the weakness and breathlessness on exertion have increased markedly. She has noticed also that her skin has become yellowish lately. She has for many years taken an iron mixture for periods of a few weeks at a time.

On 12th June, 1935, she was referred by her doctor to the Blood Clinic at Aberdeen Royal Infirmary. Blood examination showed: Hb. 55 per cent.; r.b.c. 2.56 million; C.I. 1.08; w.b.c. 4,200; reticulocytes 2.0 per cent.; cell-volume index 1.06. A film showed marked anisocytosis with many macrocytes and some small cells which were poorly stained. Differential count was: polymorphs 80 per cent.; lymphocytes 14 per cent.; eosinophils 3 per cent.; basophils 1 per cent.; monocytes 2 per cent. The icterus index was 36. Van den Bergh reaction: direct negative; indirect strongly positive. It was decided to admit her to hospital; this was done on 23rd July.

*Family history.* Father died of 'jaundice', aged 50. Mother died of 'cancer of the stomach', aged 45. One brother had 'pernicious anaemia and died of cancer' (was not in hospital). Another brother died of 'cancer'. Two sisters are alive and well. The patient has had seven children. The youngest is 25 years old and is, in her mother's opinion, anaemic.

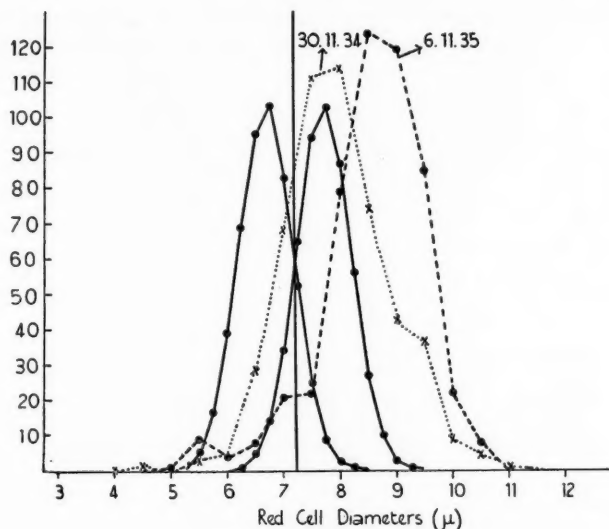
*Examination.* The patient was thin and pale and the skin had a yellowish tinge. There was a slight icteric tint in the sclerotics. The teeth were false. The tongue was completely atrophic, no papillae being visible. There were fissures at the angles of the mouth. The finger-nails were normal. There was slight symmetrical enlargement of the thyroid gland, which was of a firm consistence. *Cardiovascular system:* pulse-rate 80; blood-pressure 118/70. Apex beat in fifth left intercostal space  $4\frac{1}{2}$  inches from the mid-sternal line. There was a faint systolic murmur at all areas. Examination of the respiratory and central nervous systems showed nothing abnormal. *Abdomen:* the spleen was palpable one inch below the costal margin. The lower border of the liver lay one inch below the costal margin and was firm in consistence. Fractional test meal showed histamine-fast achlorhydria.

The patient was treated with the concentrated liver extract of Dakin as shown in Fig. (p. 45). On 1st August the icterus index had fallen to 10, and the indirect van den Bergh reaction was positive. A differential white-cell count was normal. The rise in the blood level which occurred in response to injections of liver extract was satisfactory, an increase of approximately 2,000,000 red-blood cells being obtained in four weeks as the result of the injection of 3 c.c. of anahaemin.

*Summary.* A case illustrating the transference of hypochromic microcytic anaemia to macrocytic anaemia with response to parenteral liver therapy.

*Case 2.* Mrs. J. L., aged 27. Referred by her doctor to the Blood Clinic at Aberdeen Royal Infirmary on 14th July, 1933, complaining of weakness.

*History on admission.* The patient has never been very robust, and has been in the habit of consulting her doctor periodically since the age of 16. She was always tired and easily became breathless. Iron apparently was not prescribed. Menstruation began when she was 14 years old and the loss has always been excessive. She was married five years ago and has had two miscarriages, two years and one and a half years ago. Marked loss of



CASE 2.

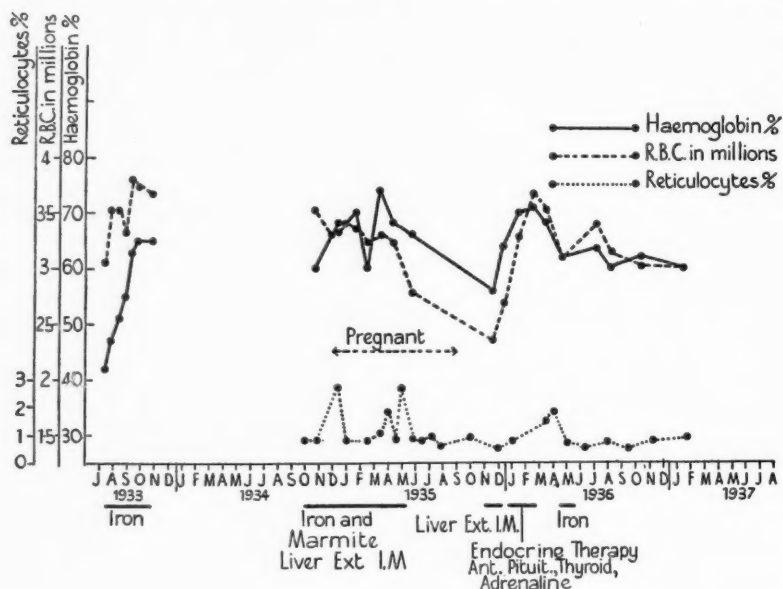
blood occurred on both occasions. Her tongue has frequently been painful and ulcerated, and during the past three years she has experienced difficulty in swallowing solids. Her diet has consisted chiefly of tea, bread, fish, porridge, and vegetable soup. No red meat has been eaten for three years. This is partly due to poor economic circumstances and partly due to the difficulty in swallowing. Two weeks ago the weakness and breathlessness on exertion increased quite suddenly without apparent cause.

*Family history.* Nothing of importance.

*Examination.* Patient was a thin, pale, tired-looking woman. The tongue was smooth and atrophic and there were fissures at the angles of the mouth. The finger-nails were thin, brittle, and spoon-shaped. There was no enlargement of the liver and spleen. Examination of the cardiovascular, respiratory, and central nervous systems, and the urine, showed nothing abnormal. Owing to dysphagia, an attempt to perform a test meal was unsuccessful. The blood Wassermann reaction was negative. The icterus index was 4. The blood count on 14th July, 1933, was: Hb. 42 per cent.; red-blood cells 3.04 millions; colour index 0.70; white-blood cells 8,600; reticulocytes less than 1 per cent. A film showed a hypochromic, microcytic type of anaemia.

Tab. ferrous sulphate (Glaxo) gr. iii, t.i.d. was prescribed. A slow improvement occurred, the blood count on 20th September being: Hb. 65 per

cent.; red-blood cells 3.75 millions; colour index 0.86. On this date it was noted that a blood film showed two distinct types of red cell: round well-stained macrocytes and hypochromic microcytes. The dose of iron was doubled, without effect on the blood count. During this time the patient



CASE 2.

felt stronger, the dysphagia became less, and the proximal parts of the finger-nails were thicker and convex. The menorrhagia continued as before.

On 2nd November, 1933, 90 gr. of iron and ammonium citrate daily was prescribed, and the patient's doctor was advised to refer her to the gynaecological department for treatment of the menorrhagia.

The patient was not seen again until 31st October, 1934. She had taken iron and ammonium citrate fairly regularly until July. Since then she had had no treatment. In May curettage had been performed and since then the blood loss during menstruation had been much less. She was still tired and breathless, and the dysphagia had increased. The tongue was atrophied, and ulcerated along the margins, and the finger-nails were thin and flattened. On 31st October, 1934, the blood count was: Hb. 60 per cent.; r.b.c. 3.52 millions; colour index 0.85. A blood film showed distinct macrocytosis and poorly stained microcytes. The Price-Jones curve gave a mean diameter of  $7.96 \mu$  (Fig. on p. 47). Ferrous sulphate tablets gr. iii, t.i.d., were again prescribed.

On 30th November, 1934, the blood count was: Hb. 66 per cent.: red-blood cells 3.31 millions; colour index 1.0; white-blood cells 6,200. The iron was then discontinued and one teaspoonful of marmite t.i.d. was taken for two weeks. At the end of this time the blood count was: Hb. 68 per cent.; red-blood cells 3.28 millions; colour index 1.05. The patient was

then given seven intramuscular injections of 5 c.c. of Campolon during the next month, and the ferrous sulphate tablets were resumed. At the end of this time, on 16th January, 1935, the Hb. was 70 per cent.; red-blood cells 3.36 millions; colour index 1.04, and macrocytosis was still marked. In February, two injections of 4 c.c. of Parenamps were given, again without effect on the blood count.

On 27th March the patient was admitted to the Aberdeen Royal Infirmary under the care of Professor L. S. P. Davidson. At this time she was four months' pregnant. Her general condition was the same, but dysphagia was absent, enabling gastric analysis to be undertaken. This showed achlorhydria in response to the gruel meal, but quite a marked response of free hydrochloric acid (30 units in one hour) occurred after the injection of histamine. Treatment with marmite and a diet consisting mainly of liver, red meat, green vegetables, and fruit juices was prescribed. This was followed by four daily injections of 4 c.c. of Hepastab. The reticulocyte percentage increased slightly to a maximum of 2.7, but no improvement in the blood picture occurred. At this time the sternum was trephined and films were made of the bone-marrow obtained. Examination of the films showed active erythropoiesis. The nucleated red cells were of all types from mature normoblasts to a type which approached closely to immature megaloblasts. The most frequent type of nucleated red cell showed characteristics midway between these extremes; the diameter was about  $10\mu$ , the cytoplasm was only partially haemoglobinized and the nucleus contained clumps of chromatin.

During her five weeks' stay in the ward the patient increased in weight from 6 st. 10 lb. to 7 st. 5 lb. and looked and felt much stronger.

On 6.11.35 patient reported at the Blood Clinic, when the blood count was: Hb. 56 per cent.; r.b.c. 2.34 millions; C.I. 1.21; w.b.c. 2,000. The macrocytosis had increased to a mean diameter of  $8.59\mu$  (Fig. on p. 47). Since the birth of a stillborn child three months previously she had had two menstrual periods with excessive blood loss. The difficulty of accepting a patient's history in regard to the degree of menstrual loss has been referred to by one of us (Fullerton, 1936). In order to estimate the actual blood loss the total iron content of the menstrual discharge during a period which she considered excessive was estimated chemically and found to be 15 mg., a figure which we believe to be a low normal.

Since iron and liver extract had failed to influence the blood picture, the patient was treated daily for fortnightly periods with extracts of the pituitary, thyroid, and adrenal glands, with equally unsuccessful results. From May 1936 to the present time, the patient has maintained without treatment a blood level of approximately 3 million red-blood cells and 60 per cent. Hb., showing the same macrocytic characteristics as previously mentioned and a leucopenia which varies from 2,000 to 6,000. The polymorphs show the greatly increased lobulation which is characteristically seen in pernicious anaemia.

*Summary.* A case illustrating the transference of hypochromic microcytic anaemia to macrocytic anaemia which failed to respond to all forms of therapy.

#### Discussion

*Group I (Cases 1 and 2).* Transference of anaemia from a microcytic to a macrocytic type has been reported by various workers (Heath, 1933; Minot, 1933). This change, however, occurs very rarely in our experience,

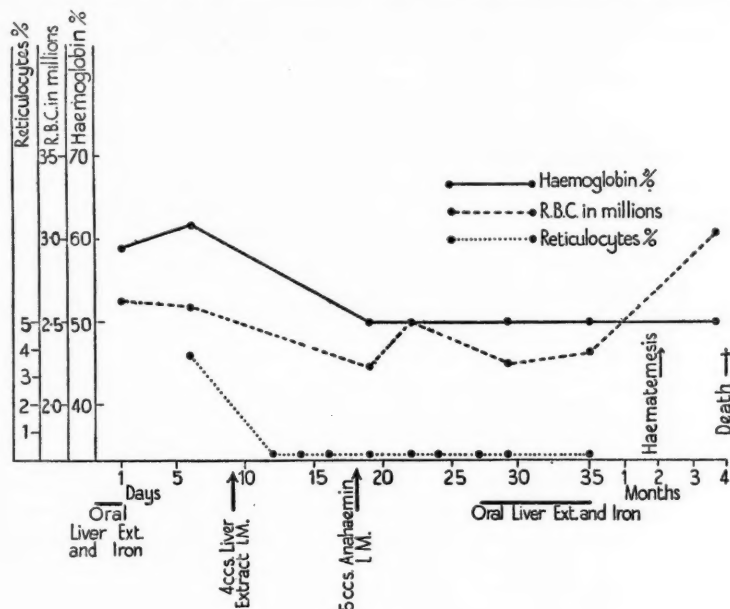
and it is for this reason that Case 1 is included in this report. During the past seven years we have investigated more than 1,000 cases of hypochromic anaemia, and despite the fact that achlorhydria was a frequent finding, in only three cases have we observed the development of severe macrocytic anaemia. The rarity of this occurrence indicates that either the cells of the stomach secreting intrinsic factor are more resistant to chronic gastritis than those secreting hydrochloric acid, or that the production of intrinsic factor by the upper small intestine is sufficient to maintain a normocytic blood picture, despite a reduced gastric secretion of the factor. In Case 1 and another case not reported, a typical response to liver extract occurred six and four years respectively after cure of the original microcytic anaemia by iron.

Case 2 is reported not only because it is an example of transference of one type of anaemia to another, but also because of its failure to respond to all forms of treatment. A study of the stained blood films revealed evidences of both forms of anaemia, namely, hypochromic microcytes and hyperchromic macrocytes. The value of the Price-Jones curve is well seen in this case. The colour index between October 1934 and March 1935 was consistently in the neighbourhood of unity, but the Price-Jones curve clearly indicated the commencement of a macrocytic anaemia which steadily increased until the pregnancy terminated in 1935. Subsequent to the pregnancy a characteristic rise in the blood level occurred, and with the improvement of gastric secretion which takes place at this time, and the withdrawal of foetal demands, the colour index returned towards unity, although the stained blood film continued to show the underlying macrocytosis. The difficulty of accepting pregnancy as the causation of the increased macrocytosis lies in the failure to obtain results from intensive parenteral administration of the anti-anaemic factor during the pregnancy. The diagnosis of this case would appear to be either semi-aplastic (hypoplastic) anaemia or achrestic anaemia (Wilkinson 1935, Israël 1936). The finding of an active red marrow in the specimen removed from the sternum by biopsy might be held to be in favour of the latter disease and to contra-indicate the diagnosis of aplastic anaemia. As this subject is fully discussed in the section devoted to Group IV, it is unnecessary at this stage to say more than that we are unable to accept this contention so easily. It is of interest that iron was as ineffective in influencing the microcytic hypochromic cells as was liver extract in remedying the macrocytosis. If this case is an example of achrestic anaemia, the achrestic character is of a double nature.

We would draw attention to the family history of Case 1, in which several members suffered from a variety of diseases of the stomach. This suggests the importance of the constitutional element in pernicious anaemia. It is of interest to note that Case 2 originally had dysphagia and spoon-shaped finger-nails, and that both of these features disappeared prior to the development of the macrocytic anaemia. Space does not permit us to discuss the extremely interesting problem of why nail changes are frequently present in severe chronic hypochromic anaemias and are extremely rare in pernicious anaemia, whereas chronic glossitis and achlorhydria are frequently present in both diseases.

*Case 3.* Mrs. A. M., aged 71. Admitted to Aberdeen Royal Infirmary, 19.6.36, with the complaint of vomiting blood during the past five days.

*History of present illness.* During the past year the patient suffered from 'indigestion' which was manifested by slight abdominal pain and by flatulence and occasional vomiting after meals. Eight weeks previously to admission she had pain across the lower chest which radiated to the right arm. This was accompanied by shortness of breath. During the past five days vomiting of blood occurred on three occasions, and melaena was first



CASE 3.

noted fourteen days previously to admission. There was some recent loss of weight.

*Family history* satisfactory. No history of anaemia in parents or brothers and sisters.

*Previous history* satisfactory.

*Physical examination.* The patient showed marked pallor without icterus. The temperature was normal. Pulse-rate on admission was 102. Blood-pressure 204/94. The cardiac rhythm was 'tic-tac'. No murmurs were heard.

*Respiratory and nervous systems.* Nothing abnormal.

*Abdomen.* The spleen was palpable about two inches below the costal margin. The lower border of the liver was three inches below the costal margin. There were no dilated superficial veins and no ascites.

*Blood examination.* R.b.c. 2.67; Hb. 59 per cent.; C.I. 1.11; w.b.c. 5,700. Differential count normal. Examination of the stained blood film showed many hyperchromic macrocytes together with poorly-stained microcytes. Icterus index 3.

*Fractional test meal.* Achlorhydria. All samples showed a trace of blood. Faeces: benzidine reaction strongly positive. Blood urea 50 mg. per cent.

The patient was treated by iron and liver extract intramuscularly,

without response. On discharge, nine weeks after admission, the blood count was: Hb. 50 per cent.; r.b.c. 2.39 millions; C.I. 1.06; reticulocytes less than 1 per cent. Three months later she was seen at her home. In the interval there had been no improvement in the general condition and she had been practically confined to bed. Another haematemesis occurred two months after discharge from hospital. On 19.11.36 the blood count was: Hb. 50 per cent.; r.b.c. 3.06 millions; C.I. 0.82; C.V.I. 0.78; w.b.c. 9,200. Death occurred two weeks later. No autopsy was obtained.

*Summary.* A case of hepato-lienal cirrhosis with haematemesis and macrocytic anaemia.

*Case 4.* W. F., male, aged 69, was admitted to Aberdeen Royal Infirmary 11.5.36, complaining of weakness and loss of weight.

*History.* For five or six weeks previously to admission the patient felt weak, easily tired, and was breathless on slight exertion. During this time he noticed increasing prominence of the abdomen and swelling of the hips, legs, and feet, especially at night. For about two years previous to this he had lost weight gradually.

The patient gave no history of jaundice. Recently he suffered from a feeling of fullness after meals which was sometimes accompanied by nausea.

*Previous history.* The patient had suffered from no major illnesses prior to the present complaint. He was never in the habit of consuming excessive amounts of alcohol.

*Family history.* Nothing of importance.

*Examination.* The patient was thin and had obviously lost a considerable amount of weight. There was moderate pallor of the mucous membranes, and dilatation of the small blood-vessels of the nose and cheeks. There was no clinical jaundice, and no atrophy of the tongue. Pulse-rate 68. Blood-pressure 122/78. The apex-beat was in the fourth left interspace,  $3\frac{1}{4}$  inches from the mid-sternal line. A soft systolic murmur was audible all over the praecordium, otherwise the heart-sounds were normal. The respiratory and central nervous systems showed nothing abnormal.

*Abdomen.* The liver dullness was markedly reduced, extending in the nipple line from the fourth to the sixth intercostal space. The spleen was not enlarged, and there was no evidence of free fluid in the peritoneal cavity. There was moderate oedema of both lower extremities and of the sacral region. The urine showed no abnormalities.

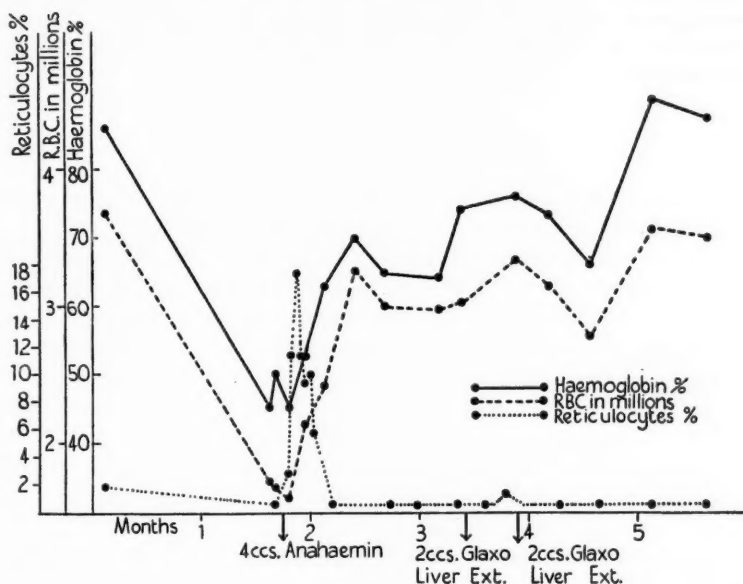
*Blood examination on admission, 11.5.36:* Hb. 50 per cent.; r.b.c. 1.68; C.I. 1.51; reticulocytes less than 1 per cent; w.b.c. 1,400. Differential count. Polymorphs 48 per cent.; lymphocytes 52 per cent. Film: macrocytic hyperchromic anaemia; moderate anisocytosis and poikilocytosis. Icterus index 3. Fasting blood-sugar 79 mg. per cent. Blood urea 32 mg. per cent.

*Stools.* Benzidine reaction negative. *Fractional test meal.* Histamine-fast achlorhydria. Excess of mucus in most of the samples.

In view of the extensive oedema and the absence of ascites, a determination of the serum protein was made. This showed a value of 4.1 gra. per cent. and the albumin-globulin ratio was 0.7:1. (Normal values: serum protein 7 per cent.; albumin-globulin ratio 3:2.)

On the basis of the marked reduction in the liver dullness and the low level of the serum protein, a diagnosis of atrophic cirrhosis of the liver with

macrocytic anaemia was made. An intramuscular injection of 4 c.c. of anahaemin was followed by a rise in the reticulocyte count which reached a maximum of 17.6 per cent. on the sixth day after the injection. On the tenth day after the injection the blood count was: Hb. 53 per cent.; r.b.c. 2.14 millions; C.I. 1.26. Ten days later it was: Hb. 63 per cent.; r.b.c. 2.42 millions; C.I. 1.31, and in another week had risen to: Hb. 70 per cent.; r.b.c. 3.26 millions, C.I. 1.08; w.b.c. 8,200. At this time the



CASE 4.

patient developed ascites and a small left-sided pleural effusion, and oedema of the legs was still present. A bromsulphthalein excretion liver efficiency test and laevulose tolerance test were carried out. In each case a normal result was obtained. The patient was then treated with a high protein diet and injections of Salyrgan. The excretion of urine increased and the oedema diminished. He was given several injections of potent liver extracts without further improvement in the blood level. The last injection was given on 31.7.36. He was discharged from hospital on 11.8.36, at which time the blood count was: Hb. 66 per cent.; r.b.c. 2.76 millions; C.I. 1.2; w.b.c. 5,000.

A fortnight after his discharge he was seen as an out-patient. He felt well and had been walking for distances of half a mile without distress. He had received no specific treatment since leaving hospital. There was no change in the liver dullness, and no evidence of free ascitic fluid. There was moderate oedema of the ankles and lower legs. Blood count: Hb. 90 per cent.; r.b.c. 3.57 millions; C.I. 1.27. Such a spontaneous rise in the blood-level is stated by several workers to occur not infrequently in cases of liver cirrhosis with macrocytosis. Since the patient objected strenuously to intramuscular injections, and since the blood-level had risen spontaneously further anti-anaemic therapy was not insisted upon.

Two weeks later (9.9.36) he was again seen as an out-patient. The improvement in his general condition was maintained and the blood count was: Hb. 87 per cent.; r.b.c. 3.50 millions; C.I. 1.24. At this time it was arranged that his private doctor should give him an injection of 5 c.c. of anahaemin at monthly intervals and an injection of Salyrgan occasionally.

The patient died at home four months after reporting at the Blood Clinic on 9.9.36. His doctor states that he was never fit for anything more than light exercise. His condition steadily deteriorated, with increasing oedema of the legs and congestion of the lungs. No autopsy was obtained.

*Summary.* A case of atrophic cirrhosis of the liver with severe macrocytic anaemia.

#### *Discussion*

*Macrocytic anaemia in disease of the liver. Group II. (Cases 3 and 4.)* The remarkably beneficial effects of liver therapy in pernicious anaemia clearly indicate the importance of this organ as the principal storehouse of the anti-anaemic factor. It has been shown that the factor is absent in the livers of untreated pernicious anaemia, but is present in the stage of remission induced by treatment (Goldhamer, 1934). Moreover, extracts made from livers obtained from patients dying with severe prolonged disease of the organ have been shown to be defective in therapeutic potency (Wilkinson, 1934). Accordingly it is not surprising that several authors (Wintrobe (1933), van Duyn (1933), Goldhamer (1934), Wright (1935), Rosenberg (1936)) have drawn attention to the finding of macrocytic anaemia in liver disease.

*Incidence.* The results of these investigations indicate that although macrocytosis is common in liver disease, a severe degree of macrocytic anaemia is rarely found. In only a minority of cases is the differential diagnosis from pernicious anaemia in doubt. On the other hand, the haematological differentiation between pernicious anaemia and the macrocytic anaemia of liver disease may be a problem of great complexity when anaemia is a prominent feature.

In a series of 12 cases of portal cirrhosis studied by Wright (1935), the colour index was greater than 1.1 in six cases, was less than 0.9 in two cases, and lay between these figures in four cases. The mean corpuscular volume was above 90 in seven cases. The average red-cell count in Wright's series was 4.04 millions. In only two cases was the red-cell count less than 3 millions. Wintrobe and Shumacker (1933) studied the case records of 138 cases of cirrhosis of the liver admitted to the Johns Hopkins Hospital. The colour index was 1.15 or higher in eight cases, and in four of these no cause for macrocytosis was found other than liver cirrhosis. Among 43 cases of hepatic disorders due to different conditions such as chronic passive congestion, cirrhosis, carcinoma, and acute yellow atrophy, macrocytosis was present in 11. Although the macrocytosis was definite, the degree of anaemia was slight or moderate, the lowest red-cell count being 2.42 millions.

In a later publication Wintrobe (1936) describes the blood findings in 132 cases of liver disease. Macrocytosis was present in 18 of 44 (40.9 per cent.) cases of cirrhosis of the liver of different types; in eight of 36 (i.e. 22.2 per cent.) cases of malignant disease of the liver, and in 17 (32.7 per cent.) of 52 cases of various other disorders of the liver. The author concluded that macrocytic anaemia was found particularly in association with liver disease of long duration and of wide extent. Rosenberg (1936) found macrocytosis in 43 of 48 (89.7 per cent.) cases of cirrhosis of the liver. In all cases the cirrhosis was widespread and mostly in an advanced stage. In only eight cases (16.7 per cent.) was the red-cell count less than 2.5 millions at any time.

*Blood Findings in Liver Disease*

Disease.	Number of cases.	Remarks.
Weil's disease (with jaundice)	3	1, no anaemia 2, hypochromic anaemia
Catarrhal jaundice	5	3, no anaemia 2, hypochromic anaemia
Carcinoma of pancreas with jaundice	2	1, no anaemia 1, hypochromic anaemia
Carcinoma of liver	1	No anaemia
Acute toxic hepatitis	1	Severe anaemia (Hb. 20 % r.b.c. 1.24 millions)
Cirrhosis of liver	16	4, no anaemia 9, hypochromic anaemia (of these 5 gave a history of haemorrhage). 3, macrocytic anaemia
Hepato-lienal fibrosis (splenic anaemia, Banti's disease)	4	1, no anaemia 3, hypochromic anaemia (all of these gave a history of haemorrhage)

During the past three years, blood examinations have been made in 32 cases of liver disease admitted to the wards of one of us (L.S.P.D.) in Aberdeen Royal Infirmary. The Table summarizes the findings. It will be noted that in only three instances was a macrocytic anaemia present, the underlying pathological condition in each case being cirrhosis of the liver. In two of these cases the anaemia was moderate in degree, viz. r.b.c. 3.11 millions; Hb. 73 per cent.; C.I. 1.18; and r.b.c. 2.82 millions; Hb. 80 per cent.; C.I. 1.43, respectively. The third case developed severe anaemia, namely, r.b.c. 1.61 million; Hb. 45 per cent.; C.I. 1.41 (Case No. 4, W.F.).

*Differential diagnosis.* Wintrobe and Shumacker (1933) have shown that the degree of macrocytosis is comparable in pernicious anaemia and in liver disease at similar erythrocyte levels. It is generally believed that the ovality in the shape of the cells, so characteristically seen in the megalocytes in pernicious anaemia, is lacking in the macrocytic anaemia of liver disease, but this is denied by Castle and Minot (1936). The same remark applies to anisocytosis. Lastly, leucopenia is frequently present both in liver disease and in pernicious anaemia. Hence it would appear to be impossible by haematological investigations to distinguish the blood pictures one from the other. It might be hoped that gastric analysis would be of

value in the differential diagnosis, since it can be assumed that intrinsic factor is lost subsequent to loss of hydrochloric acid secretion in pernicious anaemia; but even this criterion is of limited value, since in liver cirrhosis achlorhydria is frequently present, consequent on portal congestion in some cases, while in others it accompanies the chronic alcoholic gastritis which frequently precedes the liver disease. Nor can the presence of bilirubinaemia or urobilinuria be held to be of differential diagnostic value, since an increase in these conditions is found in both diseases, though for different reasons, namely, in pernicious anaemia an excessive destruction of abnormal erythrocytes, and, in liver disease, a failure of the damaged liver cells to deal adequately with the products of normal blood destruction. A history of haematemesis or the presence of enlarged veins, ascites, or gross enlargement or reduction of liver size would strongly support the view in any individual case that liver damage was the primary factor in the anaemia. Without such signs of liver disease reliance may have to be placed on the therapeutic test, namely, parenteral liver extract administration, and even this will fail to supply the correct diagnosis in a proportion of cases. Thus Wintrobe (1936) obtained no clear-cut response to liver therapy in three cases, but a maximal response was obtained in the fourth case.

Of the two cases of cirrhosis of the liver reported in this paper, Case 4 responded partially to treatment and later had a spontaneous response. Spontaneous blood remissions have been reported by several authors (Israëls, 1936; Wintrobe, 1933) and so far no satisfactory explanation for the mechanism has been advanced. An additional point of interest is that a decrease in the severity of the anaemia is not necessarily associated with general clinical improvement. Thus in Case 4 the spontaneous remission was accompanied by some clinical improvement in strength, but nevertheless death occurred from liver failure within four months of the haematological remission.

In Cases 4 and 12, and in two other cases of severe liver disease not included in this report, gross oedema was present which could not be explained by cardiac failure, renal disease, anaemia, or obstruction to the venous return by the pressure of ascitic fluid. Accordingly, we estimated the total serum protein and in every case found a low figure. Hence the oedema appeared to be due to decreased osmotic pressure in the vessels. Since the liver is believed to play an important part in the production of the plasma proteins, it is possible that a low plasma protein in the absence of massive albuminuria could be used as an indication of liver damage.

*The causation of the macrocytosis in liver disease.* A satisfactory explanation of the cause of the macrocytic blood picture which occurs in certain cases of disease of the liver is lacking. In the first place, while it is generally true that the most marked examples of macrocytic anaemia are reported in advanced cases of liver disease, a study of the case reports in the literature makes it clear that this blood pattern does not occur at any definite period in the progressive downward course of portal cirrhosis, nor

does it depend on the degree of obstruction to the portal circulation. We have had cases reporting to the wards for paracentesis at fortnightly intervals for periods of months and sometimes years, in which anaemia was neither macrocytic in type nor more than mild to moderate in degree. Of the 12 cases reported by Wright (1935), Case 12 had symptoms of longer duration and the consequences of portal obstruction were more marked than in any of the other cases, and yet the erythrocyte count was 4.6 millions with a colour index of 0.81.

The following explanations for the macrocytosis require consideration:

1. Defect of storage of the anti-anaemic factor in liver.
2. Defect in the final stage of its synthesis or elaboration in the liver.
3. Defect in production of intrinsic factor or defect in absorption of the interaction product.
4. Depressant effect on bone-marrow of toxic products formed or retained as the result of liver failure.

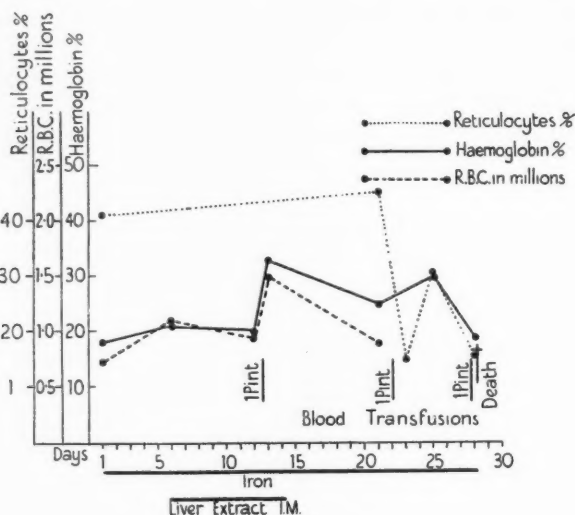
If the hypotheses mentioned under the headings (1) and (3) were admitted, then parenteral administration of liver extract should be efficacious, and since this does not occur in the majority of cases, such an explanation which at first sight appears so obvious, must be dismissed. Minot (1936) is in favour of cause 4, but his explanation does not appear to be entirely satisfactory, either to us or to certain other workers. Toxic retention in general depresses the function of the bone-marrow and produces a blood picture characteristic of semi-aplastic anaemia, in which the blood level falls with little change in the appearance of the erythrocytes. Thus a macrocytic anaemia is in our experience an unusual finding in kidney disease, even in the terminal stage when nitrogen retention is a prominent feature. It is for this reason that we favour the view that the liver plays a more important part in haemopoiesis than merely storing the anti-anaemic factor, and that it takes some as yet undiscovered part in its final synthesis.

Finally, our object in reporting these two cases of macrocytic anaemia due to cirrhosis of the liver is, firstly, because of the severity of the anaemia present, which is comparable to that seen in the severe relapse stages of pernicious anaemia, and in contradistinction to the mild degree of macrocytic anaemia accompanying liver disease reported in the literature. Secondly, we wish to emphasize the vastly different prognosis between these two types of macrocytic anaemia. While the outlook for a case of pernicious anaemia is to-day excellent, the prognosis of macrocytic anaemia secondary to liver disease is extremely bad. Prognosis should be based on the evidence available of the degree of liver damage present, the macrocytic blood picture being considered merely as one of the indications of the severity of the underlying disease. Accordingly, if clinical signs are found in a case of macrocytic anaemia suggesting the possibility of liver disease, it is unwise to commit oneself to prognosis until the effects of the parenteral administration of a potent liver extract have been assessed for some time.

*Case 5.* Mrs. C. H., aged 56. Admitted to Aberdeen Royal Infirmary on

24.4.35, under the charge of Dr. J. A. Innes, because of progressive weakness and jaundice.

*History.* About thirteen months ago the patient noticed that her eyes and skin were slightly yellow, and she was breathless on exertion. Since then the jaundice has gradually progressed, and weakness, breathlessness, and palpitation have become more marked. For two weeks before admis-



CASE 5.

sion these symptoms became so severe that she was unable to work, and vomiting of dark slimy material occurred on several occasions.

*Previous history.* The patient had an attack of jaundice when she was 7 years old. She does not remember the details of this illness. Apart from this she has always been healthy.

*Family history.* There was no family history of jaundice, gall-stones, or anaemia.

*Examination.* Patient was a thin, obviously anaemic, and deeply jaundiced woman in a very exhausted state. The skin was a dark lemon colour and the conjunctivae were deep yellow. The teeth were false. The tongue was slightly furred.

On admission the temperature was 98.6° F. and the pulse-rate 110. Thereafter, the temperature ranged irregularly between 97.4° and 101.6° F., and the pulse-rate was usually between 90 and 100. *Cardiovascular system:* The apex-beat was in the fifth left space  $4\frac{3}{4}$  inches from the mid-sternal line. There was a systolic murmur at all areas. Blood-pressure was 102/50. *Abdomen:* rather prominent. The spleen was grossly enlarged, reaching to within two fingers' breadths of the umbilicus, and was very firm in consistence. The liver was enlarged and firm; its lower border was three inches below the costal margin. The epigastric veins were distended. Nothing of importance was noted on examination of the respiratory and central nervous systems. The urine contained bile pigments and a large amount of urobilinogen.

*Blood examination* (26.4.37). Hb. 18 per cent.; r.b.c. 0.70 million; C.I. 1.28; w.b.c. 12,200; reticulocytes 42 per cent. The red cells showed a tendency to clumping which rendered an accurate cell count difficult. The clumping, however, was not so marked that counts had to be done at body temperature. There was considerable anisocytosis. All the cells were well stained. Many round macrocytes and microcytes were present; a few normoblasts were seen. Icterus index 100. Van den Bergh: delayed direct reaction; positive indirect reaction. Fragility test 26.4.35. A great increase in fragility of the red-blood cells was present, since haemolysis started at 0.7 saline.

*Test meal* (26.4.35). The specimens were very difficult to obtain and consisted only of a few c.c. of bile-stained material. A trace of free hydrochloric acid was present in the 1½- and 2-hour samples. No blood was present.

Treatment with intramuscular injections of Campolon and large doses of Ferri et Ammon. Cit. was instituted. No improvement in the blood count occurred. The slightly beneficial effect of two blood-transfusions is seen in the chart. In spite of the high percentage of reticulocytes the count remained at a very low level. During a third blood-transfusion given in preparation for splenectomy on 25th May the patient became unconscious and died.

Post-mortem examination twenty-four hours after death.

*Liver.* The liver shows an extensive portal cirrhosis. There is a slight patchy infiltration of the fibrous tissue but no increase in the number or dilatation of the bile-ducts. The portal veins appear to be reduced in calibre. In the liver parenchyma there is only a moderate amount of pigment.

*Spleen.* The lymphoid tissue is well marked but is rather diffuse. No active germ centres were encountered and the central arteries showed only a minor degree of thickening. A moderate increase in the quantity of pulp had resulted from a packing of the tissue with red-blood corpuscles. This had led to compression of the sinuses until they resembled young capillaries. Neither a fibrosis nor an increase in phagocytosis could be demonstrated.

The appearances of the liver and spleen are consistent with portal cirrhosis of the liver and acholuric jaundice.

*Summary.* A case of acholuric jaundice with portal cirrhosis of the liver and severe macrocytic anaemia.

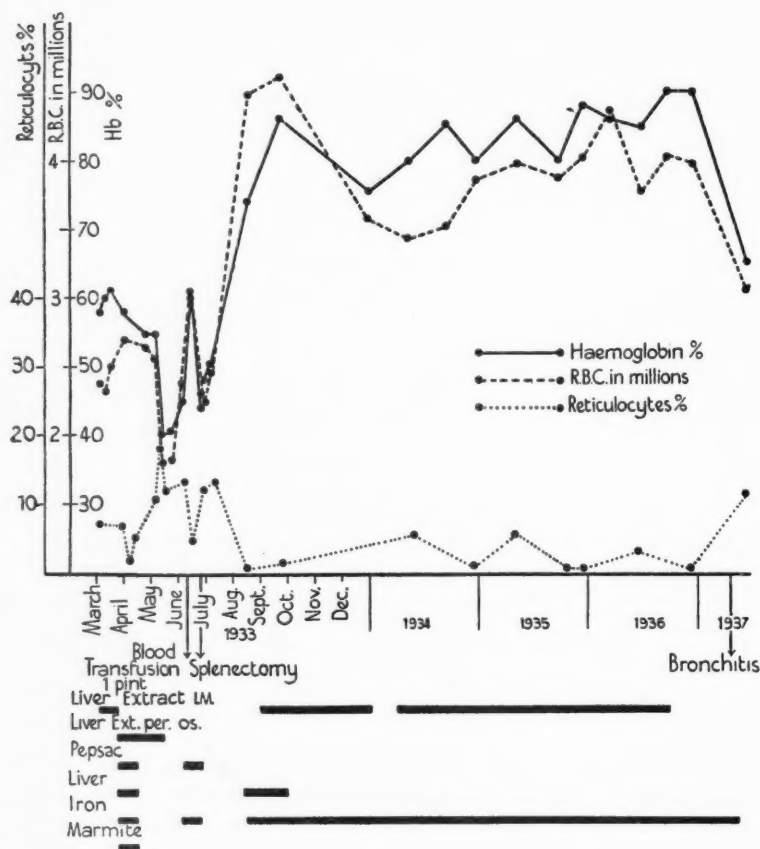
*Case 6.* Mrs. C. L., aged 61 years. Referred by her doctor to the Blood Clinic, Aberdeen Royal Infirmary, on 23rd February, 1933, complaining of weakness.

*History.* About nine months ago the patient began to feel weak, and breathlessness and palpitation were readily brought on by exertion. These symptoms increased until two months ago, and since then she thinks she has become a little stronger. She has never noticed any jaundice, and has had no sore tongue. There have been no subjective sensory symptoms. There has been no recent blood loss, and the menopause occurred sixteen years ago. All her life she has suffered from occasional attacks of sickness, followed by bilious vomiting.

*Previous history.* Patient has always been a healthy woman and has had no major illnesses since childhood.

*Family history.* Patient has had four children; the youngest is 28 years of age. All are healthy. No family history of anaemia or jaundice was obtainable.

Physical examination revealed a well-nourished woman with moderate pallor and no icterus. *Cardiovascular system*: apex-beat: fifth left interspace  $3\frac{3}{4}$  in. from mid-sternal line. No murmurs. Blood-pressure 196/120. *Abdomen*: no enlargement of liver and spleen; no tenderness or rigidity. Examination of the respiratory and nervous systems was entirely negative. Urine: urobilinogen positive; albumin and sugar



CASE 6.

absent. Faeces: benzidine test negative. No steatorrhoea. Fractional test meal. Histamine-fast achlorhydria. Large excess of mucus in all samples. Fasting juice 5 c.c.

*Blood examination 2.3.33*: Hb. 58 per cent.; r.b.c. 2.39 millions; C.I. 1.23; mean diameter  $7.94 \mu$ ; reticulocytes 7.4 per cent.; w.b.c. 7,200. Film. Red cells well stained, moderate macrocytosis present. Occasional polychromasia and punctate basophilia. Icterus index 10. Van den Bergh reaction: positive indirect, negative direct. On 28.3.33 a fragility test showed a slightly increased fragility of the patient's red cells, as compared with a control; patient 0.45 saline, control 0.40.

A tentative diagnosis of pernicious anaemia was made, and 4 c.c. of Hepatex I.M. were injected intramuscularly every third day, with no definite improvement. The course of the blood count is shown in the Chart. The patient was then treated by Filivex, a very potent oral fish-liver extract, in a dose of  $7\frac{1}{2}$  grm. t.i.d. for eleven days, with equally ineffective results. A course of treatment with oral liver extract (B.D.H.) was then given, lasting sixteen days—again without effect on the blood level. The diagnosis of pernicious anaemia had by now been discarded in place of a macrocytic haemolytic anaemia, and the patient was admitted to the wards of Professor L. S. P. Davidson on 25th April, 1933, for full investigation. On 27th April the icterus index was 15, and the van den Bergh test showed a positive indirect and a negative direct reaction. Another fragility test was done, and on this occasion no increase could be shown. Simultaneous treatment with Pepsac, liver extract, whole liver, iron, and marmite was begun. The reticulocyte count increased, but the Hb. and red-cell levels fell. The icterus index rose, reaching 33 on 5th May, and the spleen became palpable on 10th May. It was evident that a haemolytic crisis had developed.

The patient was discharged from the ward on 19th May, and it was arranged for her to return for splenectomy when the blood count had improved. At home she continued treatment with whole liver, Pepsac, and iron.

The patient was re-admitted on 3rd June. There was little change in the physical condition. The spleen was still palpable and there was slight jaundice. On 5th June the blood count was: Hb. 45 per cent.; r.b.c. 2.38 millions; C.I. 0.96; w.b.c. 7,800; reticulocytes 13.6 per cent. Icterus index 20. Van den Bergh positive indirect reaction, delayed positive direct reaction. On 10th June patient was given a blood-transfusion. This raised the blood level, but in the following nine days it fell to its previous level. Splenectomy was performed by Professor J. R. Learmonth on 23rd June. The spleen was enlarged to the costal margin and adherent to the diaphragm. There was very little bleeding and a blood-transfusion was not necessary. The patient made a good recovery and was discharged on 12th July. Thereafter, she continued to report to the Blood Clinic as an out-patient. The marked improvement which followed splenectomy is shown in the Chart. Since then the patient has reported regularly at monthly intervals. An injection of 4 c.c. of Hepastab or Campolon has been given monthly. In addition the patient has taken whole liver, Pepsac, and iron. The blood count has remained at approximately the same level: Hb. about 80 per cent. and red cells a little under 4 millions. The reticulocytes have varied from less than 1 to 7.7 per cent. A few representative counts are shown in the Chart. The icterus index has increased from 5 in December 1933, to 9 in September 1935. Her health is moderately good; she is able to do light housework and leads a fairly full life. She is still rather easily tired.

The patient reported again on 9th June, 1937. She stated that she had had an attack of bronchitis six weeks before and since then she had felt weaker. After the attack of bronchitis she had noticed a yellowish tinge of the face and eyes.

*Blood examination:* Hb. 65 per cent.; r.b.c. 3.07 millions; C.I. 1.07; reticulocytes 11.6 per cent.; w.b.c. 14,200. The red cells showed increased anisocytosis, macrocytosis, and hyperchromia. Icterus index 40. Van den Bergh reaction: faint delayed direct; strong immediate indirect. Urine:

urobilinogen positive. There appears to be little doubt that the infective illness caused a definite increase in the haemolytic process.

Report on spleen removed at operation 23.6.37. The Malpighian corpuscles are rather smaller than is usual and they are widely separated by an increase in the quantity of pulp tissue. Some of the Malpighian corpuscles have active germ centres, and in nearly all the central artery is somewhat thickened. The increase in the pulp tissue is due to excessive numbers of red-blood corpuscles being present. These choke the pulp tissue and appear to compress the sinuses so that their lumina are considerably reduced. Amongst the red corpuscles are many normoblasts. The reticulum fibres are increased in number but are separated by the erythrocytes. No increased phagocytic activity was observed, but large quantities of pigment were present in the form of coarse brown granules.

The appearances are consistent with the usual findings in acholuric jaundice.

*Summary.* A case of acquired haemolytic jaundice with severe macrocytic anaemia.

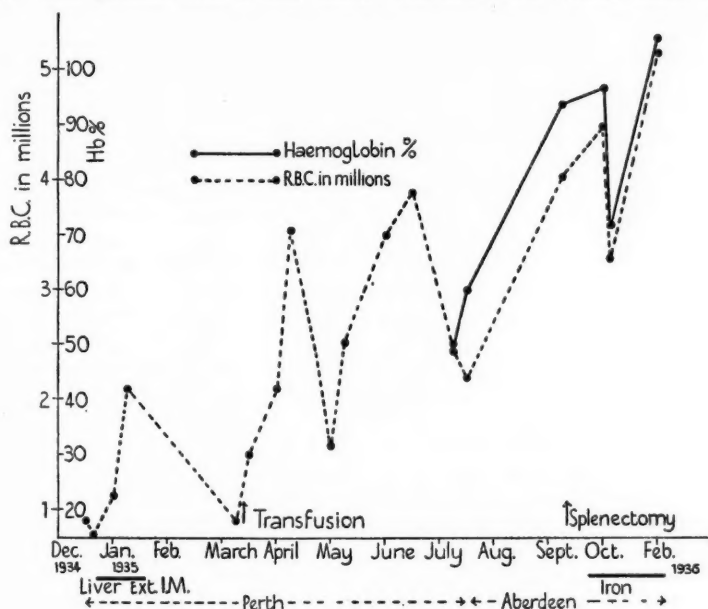
*Case 7.* T. B., male, aged 25 years. Shop assistant. Admitted to Aberdeen Royal Infirmary under one of us (L.S.P.D.) on 22nd July, 1935, complaining of jaundice and weakness.

*History of previous health and present illness.* About three years previously to admission the patient began to have attacks of faintness. These came on practically every evening after the day's work was over. On Sundays and on holidays he was free from attacks. He did not lose consciousness but felt faint and dizzy. These attacks passed off when he took anything to eat or drink, and he attributed the attacks to hunger. He never had an attack during the day. During an attack he regurgitated mouthfuls of white frothy material. Ten months ago he noticed that his eyes were becoming yellow and he began to have pains in the middle of his back. At the same time he noticed that his urine was darker in colour, but his stools were not clay-coloured. He went to bed for a week and at the end of this time he felt quite well and returned to work. He then became very easily tired and had a constant feeling of sickness. At the end of October 1934 these symptoms had increased to such a degree that he stopped work and kept to bed for two months. Weakness increased markedly during this time, but he noticed no increase of the yellow colour of his eyes and did not think that his skin was jaundiced.

At the end of December 1934 he was admitted to the Royal Infirmary, Perth, under the charge of Dr. Ronald Paton. A few of the blood counts which were done while he was in that Institution are shown in the chart. A blood film on 25.12.34 was reported as being 'consistent with pernicious anaemia'. Treatment with Campolon injections was carried out. As can be seen from the chart, marked improvement in the red-cell count occurred. He was discharged on 16.1.35 with a red-cell count of 2.11 millions, but was re-admitted on 6th March with a blood count almost identical with that present on his first admission. On 17th March a blood-transfusion was performed and injections of Campolon were recommenced. Red-cell counts during the next four months showed considerable fluctuation. In a report which was sent from the Royal Infirmary, Perth, it was stated that the patient had frequent attacks of acute epigastric pain which lasted a few minutes. These preceded a drop in the red-cell count and the accompanying increase in jaundice. During this period Campolon injections were continued and Bland's pills were also prescribed.

**Family history.** Father alive: has never been jaundiced but was operated on for gall-stones six years ago. Mother alive and well. Paternal grand-parent had jaundice (cause unknown). One brother and three sisters alive and well; none gives a history of jaundice or anaemia.

**Examination** (on admission to Aberdeen Royal Infirmary on 22nd July, 1935). The patient was a tall, fairly well-nourished young man, with a



CASE 7.

marked icteric tinge of the skin and sclerotics. The tongue was moist and not atrophic. The upper teeth were false; three lower teeth were very carious. The finger-nails were normal. Both tonsillar glands were enlarged, otherwise no glandular enlargement was present. The temperature was slightly subnormal. **Cardiovascular system:** pulse-rate 105. Blood-pressure 130/80. There was no enlargement of the heart and no murmurs were present. The respiratory and central nervous systems showed nothing abnormal. **Abdomen:** the lower border of the liver was half an inch below the costal margin. There was no tenderness over the gall-bladder area. The spleen was enlarged; the edge lay three fingers' breadths below the costal margin. The consistence was firm but not hard. Urine examination showed a strong positive urobilinogen reaction but no other abnormal findings.

**Blood examination.** Hb. 60 per cent.; r.b.c. 2.22 millions; C.I. 1.36; w.b.c. 4,600; reticulocytes 20 per cent. Cell-volume index 1.28. Icterus index 30. Van den Bergh reaction: positive indirect. Fragility tests of the patient and of his father and mother were done.

	Patient.	Father.	Mother.
0.35	+++	+++	++
0.40	++	++	+
0.45	++	trace	trace
0.50	+	0	0
0.55	0	0	0

A slight but definite increase in the fragility of the patient's red cells was therefore present. A diagnosis of acholuric jaundice was accordingly made and the patient was discharged on 24.7.35, with a view to re-admission later for splenectomy.

He was re-admitted on 14th September. In the interval he had taken Tab. Ferrous Sulph. gr. iii t.i.d. He now felt much stronger and the icterus had gradually disappeared. The spleen had decreased in size and was just palpable at the costal margin.

*Blood examination.* Hb. 92 per cent.; r.b.c. 4.04 millions; C.I. 1.14; w.b.c. 5,400; reticulocytes 2.5 per cent. Cell-volume index 1.13. Icterus index 15. Van den Bergh reaction: positive indirect. On 16th September splenectomy was performed by Professor J. R. Learmonth. There were few perisplenic adhesions and the viscus was easily mobilized. The splenic artery consisted of three branches which rendered ligation of the pedicle difficult. The gall-bladder contained eight hard stones which were so small that they were not removed.

On 3rd October the blood count was very satisfactory: Hb. 97 per cent.; r.b.c. 4.45 millions; and the reticulocytes had fallen to less than 1 per cent. On 6th October, however, the blood count had fallen to: Hb. 72 per cent.; r.b.c. 3.42 millions; C.I. 1.06; w.b.c. 12,200. The fragility test was normal. He refused to remain longer in the ward and returned home that day.

Patient reported as an out-patient on 16.2.36. He gave the following history: on his return home he felt very well and has been in perfect health since. He thinks his eyes are still slightly yellow but this has never been more marked than it is now. He has had no abdominal pains, sickness, weakness, &c., and is quite fit for a full day's work. He had taken Tab. Ferrous Sulph. 1 t.i.d., p.c., until a week ago.

Examination revealed a yellowish tinge of the sclerotics. The liver edge was firm and was palpable half an inch below the costal margin.

*Blood examination.* Hb. 106 per cent.; r.b.c. 5.24 millions; reticulocytes less than 1 per cent.; w.b.c. 6,250; C.V.I. 1.02. Differential count normal. Film showed slight anisocytosis and a few macrocytes and polychromatic cells. Fragility test showed that haemolysis started at 0.6 per cent. compared with the control reading of 0.45 per cent. An increase in fragility following splenectomy was a surprising finding. The icterus index was 30, and the van den Bergh reaction gave a strongly positive indirect result.

*Test meal.* Complete histamine-fast achlorhydria. In view of these findings it was considered that a hepatitis was present secondary to gall-stones and infection of the biliary tract, which indicated the need for surgical drainage of the gall-bladder. The patient, however, refused operation. On 7.3.37 his doctor reported that he was in perfect health and was quite able for full-time work. Two blood counts were done during 1936; on both occasions the red cells exceeded 5 millions per c.mm.

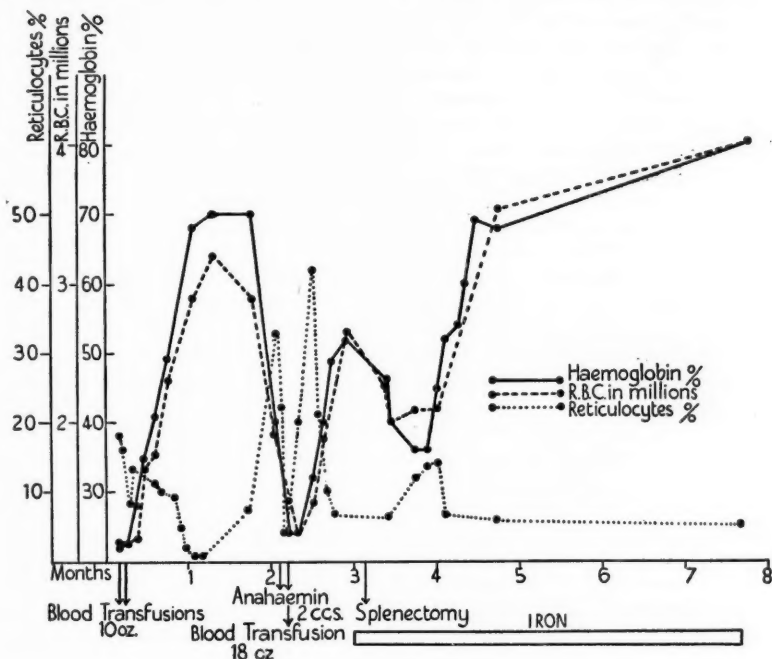
Report on spleen and section of liver removed at operation 16.9.35:

*Liver.* No definite cirrhosis could be shown, although in many of the portal tracts there was a slight degree of round cell infiltration and in several lobules cells with double nuclei suggested regenerative changes. A slight excess of bile pigment was present in the parenchymatous cells.

*Spleen.* The Malpighian corpuscles were prominent but rather widely separated. Most of them contained large germ centres throughout which there was a coarse hyaline reticulum probably representing a degenerative change. The central arteries were slightly thickened. The pulp was increased in amount and the tissue was packed with red-blood corpuscles but

not to the extent of compressing the venous sinuses which are still well defined. Much pigment in the form of coarse brown granules was present both in the pulp and in the germ centres, but phagocytosis was not a prominent feature. The tissue is in keeping with a diagnosis of acholuric jaundice.

*Summary.* A case of acquired acholuric jaundice with macrocytic anaemia. The case illustrates several previous haemolytic crises.



CASE 8.

*Case 8.* Mrs. E. R., aged 25, was admitted to Aberdeen Royal Infirmary on 21st September, 1936.

*Complaint.* Fainting turns, breathlessness, and palpitation.

*Family History.* Satisfactory. No history of anaemia or jaundice in parents or brothers and sisters. Patient has had three children, all of whom are alive and well.

*Previous history.* Satisfactory until seven months ago.

*History of present illness.* In February 1936 patient suffered from pains in the joints and back and felt feverish. She was not confined to bed at this time. Since then she has been breathless on exertion, and palpitation and giddiness have been frequent. She has noticed swelling of the feet and hands, most marked in the mornings, and there has been a numb feeling in the fingers of both hands.

During the four days prior to admission the patient fainted three times. She believes she was unconscious for five to ten minutes. Nausea and bilious vomiting also occurred.

*Examination.* The patient was well-nourished, extremely anaemic, and

moderately jaundiced. She was desperately ill and sweated profusely. The pulse-rate was 124 per minute, the respiration rate 30 per minute. The temperature varied from 103 to 105 in the first 48 hours. The blood-pressure was 120/60 on admission, and fell on the fifth day to 100/48, the pulse being very poor in quality and the heart-sounds distant and weak in character. Nothing of importance was noted on examination of the respiratory and central nervous systems. The spleen was palpable three fingers' breadths and the liver two fingers' breadths below the costal margin. Enlarged lymphatic nodes were present in both axillae and in both posterior triangles of the neck.

*Urine.* The amount excreted daily was small. A trace of albumen and a large amount of urobilinogen were present.

Blood examination on admission was as follows: r.b.c. 1.12 millions; Hb. 23 per cent.; C.I. 1.05; reticulocytes 18 per cent.; w.b.c. 5,200. Differential count: myelocytes 2 per cent.; metamyelocytes 42 per cent.; polymorphs 20 per cent.; lymphocytes 36 per cent. Film. Macrocytosis and hyperchromia present. Marked polychromasia. Fragility test normal. Icterus Index 60. Blood urea 37 mg. per cent. Van den Bergh reaction delayed direct and positive indirect.

The case was diagnosed as one of acquired haemolytic anaemia in a severe crisis. We have previously had under our charge a case similar in many respects to the one described, in whom a fall of the blood count from 5 to 1 million in a few days was accompanied by a rise of the temperature to 105°, vomiting and collapse. Fortunately a blood culture was made in the present case, and an organism of the *Salmonella* group, Dublin type, was grown in pure culture. Cultures of the faeces were repeatedly positive for this organism.

*Course of the disease.* The patient was immediately given a transfusion of 10 oz. of blood, and this was repeated on the following day. These small quantities were deliberately given in view of our experience of dangerous reactions in haemolytic anaemias. Severe haemolysis was proceeding, as was evident from the fact that the blood-level had fallen slightly after the transfusions. The clinical condition slightly improved. The temperature fell by the fifth day to 99°F. and swung between this point and 100°F. for another ten days before a normal level was maintained. By the end of the first week the blood count was still stationary at approximately 1 million red cells, while the reticulocytes consistently remained at more than 10 per cent.

With the subsidence of the fever at the end of the second week the patient's clinical and haematological condition steadily improved and she was discharged to the Convalescent Home at the end of the fifth week, with a blood count of: r.b.c. 3.2 millions; Hb. 70 per cent.; C.I. 1.09; reticulocytes 1 per cent.; w.b.c. 6,000. The lymphatic nodes which, during the course of the acute illness, had been found to be enlarged in many places, were still palpable but were smaller and firmer, while the edge of the spleen just reached the costal margin.

*Second admission 18.11.36.* Approximately one month after discharge the patient began to feel weak and out of sorts. She had attacks of sickness, diarrhoea, and abdominal pain, and was breathless on the least effort. She noticed she had rapidly become paler and jaundiced.

On examination symptoms and signs identical with those already described on the first admission were present, but to a less degree, namely, enlargement of the liver, spleen, and lymph nodes, bilirubinaemia, urobilinuria, and fever which reached a maximum of 101.8° and continued for ten days. Blood examination on admission was as follows: r.b.c. 1.9 millions; Hb. 40 per cent.; C.I. 1.05; reticulocytes 33 per cent., and w.b.c. 9,400.

Macrocytosis was still present. Icteric index 25. Van den Bergh reaction: positive delayed direct and indirect reactions. The faeces were still positive on culture for the same organism. Five days later the clinical condition was much worse, the pulse-rate being 110 and the blood-pressure 110/54, while the Hb. had fallen to 24 per cent. A positive agglutination was obtained at a dilution of 1:3400 between the patient's serum and the *Salmonella* organism, Dublin strain. Accordingly a transfusion of 18 oz. of blood was given very slowly, with some improvement in the general condition, but with no change in the blood level. The patient, however, slowly improved and three weeks later, when the red cells had reached 2.5 millions and the Hb. 54 per cent., she was transferred to Professor J. R. Learmonth's ward for splenectomy, which was undertaken on the following day after injection of 20 c.c. of the patient's blood into the buttock. Before ligating the splenic artery, 1 c.c. adrenaline was injected subcutaneously to empty the engorged organ of its contained erythrocytes. A blood count made twenty-five minutes after the injection showed a rise in the red-cell count from 2.63 to 3.40 millions per c.mm.

Contrary to our expectation, a haemolytic crisis again occurred after the operation, as manifested by clinical jaundice, marked urobilinuria, a rising reticulocyte count, and a falling blood level. It was not until three weeks after operation that the clinical and haematological state of the patient began to improve, but it then improved rapidly, so that forty days after the operation the Hb. reached 69 per cent. and the red-cell count approximately 3.5 millions, at which time the patient was discharged home in good health.

About five weeks later (5.3.37) the patient reported to the Blood Clinic and stated that she felt well and was able to do her housework. Clinical jaundice was absent: the edge of the liver was palpable 1 in. below the costal margin and tenderness was elicited over the gall-bladder. Many enlarged lymph nodes were palpated, particularly in the posterior triangles of the neck. The blood count was approximately the same as when she was discharged. The reticulocytes were still increased, viz. 6.8 per cent. The icterus index was 12 and the van den Bergh reaction gave a positive indirect result.

On 9.6.37 the patient again reported at the Blood Clinic. She stated that she felt in good health and was able to do a full day's work without discomfort and had noticed no jaundice or diarrhoea. On examination the liver was palpable 1 in. below the costal margin, with some persistent tenderness over the region of the gall-bladder. The lymph nodes were still enlarged and firm. The blood count showed a moderate improvement, viz. r.b.c. 3.91 millions; Hb, 79 per cent.; C.I. 1.01; reticulocytes 5.8; w.b.c. 6,200. Icterus index 20. Blood film showed cells well stained and round; moderate anisocytosis, but no definite macrocytosis. Van den Bergh reaction indirect positive. Fragility test showed slight increase.

*Report on spleen removed at operation:* the microscopic appearances were characteristic of acholuric jaundice.

*Summary.* A case of acute haemolytic macrocytic anaemia with *Salmonella* (Dublin strain) infection. Splenectomy was followed by recovery.

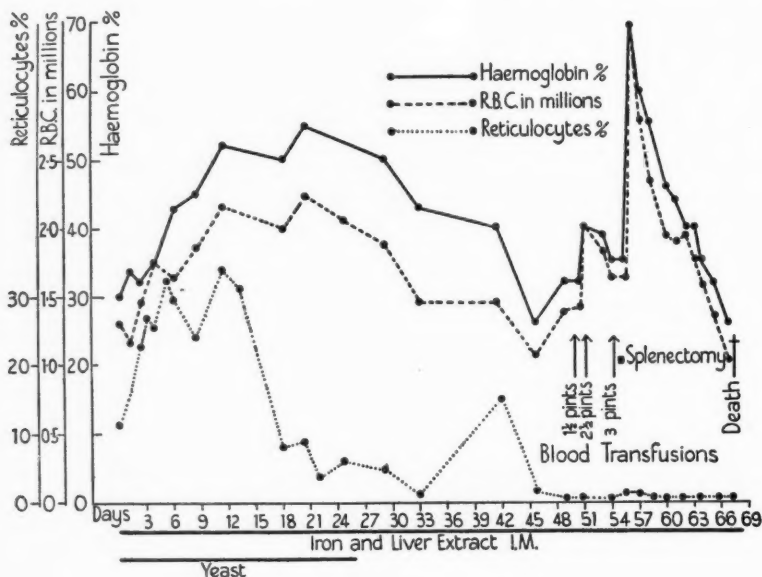
*Case 9.* Mrs. M. M., aged 51. Admitted to Aberdeen Royal Infirmary 3.9.36.

*Complaint.* Great exhaustion, weakness, and breathlessness.

*Family history.* Satisfactory. No history of anaemia or jaundice in parents or brothers and sisters. Patient has had no children or miscarriages.

*Previous history* satisfactory until two years ago.

*History of present illness.* Two years ago patient noticed that she was more easily tired and made breathless on effort. During the past eight months these symptoms have become more marked, the appetite has become poor, and there has been loss of weight. Recently she has noticed that she has become steadily paler and that the abdomen was distended. She has never complained of gastric symptoms other than loss of appetite, or of



CASE 9.

colicky pains suggesting gall-stones, nor has she noticed the presence of jaundice. No history of haematemesis, urinary troubles, glossitis, or uterine bleeding, since the periods stopped two years ago.

The patient had never been abroad.

*Physical examination.* The patient was a middle-aged woman whose nutrition was satisfactory despite the history of previous loss of weight. She was extremely pale. A slight icteric tint was visible in the eyes. She looked very ill and exhausted, was restless and feverish, irregular temperature up to 102° F. being present.

*Cardiovascular system.* The cardiovascular manifestations were in keeping with severe anaemia, viz. slight dilatation of the heart, low blood-pressure, (115/55), rapid pulse, and blowing systolic murmurs at all areas. Moderate oedema of ankles and back was present.

*Respiratory system.* Apart from crepitations at the bases of both lungs, nothing abnormal was found.

*Nervous system.* Nothing abnormal was found.

*Urinary system.* Apart from a trace of albumen and the presence of large amounts of urobilinogen, nothing abnormal was found in the urine.

*Alimentary system.* Tympanitic distension of the bowels was continually present. The liver was palpable three fingers' breadths below the costal margin and the spleen two to three fingers' breadths below the costal margin.

There was no tenderness on palpation. The organs felt firm and smooth to the touch. The benzidine test for occult blood in the faeces was negative.

*Test meal.* Fasting juice 30 c.c. Free HCl 0. Combined acid 10. 0.5 mg. histamine injected. Fifteen minutes: copious clear juice. Free HCl 100. Combined acid 16. Thirty minutes: Free HCl 126. Combined acid 15. No blood present.

*Radiological examination* of the alimentary tract revealed no organic disease, but barium hurried through the stomach and small bowel, reaching the colon in six hours. The enlarged spleen could be easily seen in the X-ray plates.

*Lymphatic system.* No enlargement of lymphatic glands.

*Blood examination* 4.9.36. Hb. 33 per cent.; r.b.c. 1.30 millions; C.I. 1.27; C.V.I. 1.30; w.b.c. 11,200; reticulocytes 15.8 per cent.; platelets very scanty. Film. Marked anisocytosis, macrocytosis, and hyperchromia. Icterus index 12. Van den Bergh reaction: indirect and biphasic reactions positive. Ehrlich's aldehyde test for urinary urobilinogen strongly positive. The fragility of the red cells was less than that of a normal control. Patient: haemolysis started 0.4 per cent. Control: haemolysis started 0.45 per cent.

A blood count done by another pathologist previously to the patient's coming under our charge showed the following result:

29.8.36. Hb. 44 per cent.; r.b.c. 1,586,000; C.I. 1.4; w.b.c. 3,460.

*Course of the illness.* Despite the presence of a severe macrocytic anaemia, together with reticulocytosis after injection of liver extract, the gross enlargement of liver and spleen appeared to be such an important feature that we informed the patient's doctor that this did not appear to be a straightforward case of pernicious anaemia. This opinion was later maintained because of the following features:

1. The prolonged and continuous reticulocyte response.
2. The maintenance of an increased icterus index, which usually falls rapidly in pernicious anaemia after the reticulocyte response.
3. The great enlargement of the liver and spleen.
4. The development of free fluid in the abdomen.
5. The gross oedema of the ankles. In uncomplicated cases of pernicious anaemia in relapse the degree of oedema is usually slight.

The patient showed an extreme haemorrhagic tendency, large bruises occurring at points of pressure and at the sites of injection. Marked thrombocytopenia was present.

The blood counts are shown in the chart. The first response to anahaemin appeared to be satisfactory, for it produced a marked rise in the reticulocyte count and an increase in the red-blood cell count of 1 million in ten days, with improvement of the clinical symptoms. The result, however, was temporary, for, in spite of treatment with anahaemin, iron, and yeast, the blood count steadily fell, reaching approximately 1 million cells on 19th October, 1936. Coincidentally the icterus index remained at a high level (15 to 20) with a positive indirect van den Bergh reaction, and urobilinogen was constantly present in the urine in large amounts. The free fluid could be easily demonstrated in the abdomen, and the oedema of the legs, which had been markedly reduced, steadily increased. This oedema could not be accounted for by anaemia, cardiac failure, or loss of albumen in the urine, hence estimation of the plasma protein was made and was found to be greatly reduced (4 per cent.). Although it was felt that the raised level of serum bilirubin, ascites, and low plasma protein all indicated that the liver was the primary seat of the trouble, it was possible that

excessive blood destruction was occurring in the spleen coincidentally. Four pints of blood were given intravenously on 22nd and 23rd October, with little improvement other than an increase in the platelet count. Accordingly it was decided to perform splenectomy, since the patient was desperately ill despite all forms of anti-anaemic treatment. This was carried out by Professor Learmonth on 29th October, following transfusion of three pints of blood. No beneficial results occurred, and the blood count steadily fell from the high level of 3.46 millions on the day of transfusion to 1 million ten days later, when the patient died. Following splenectomy there occurred a marked increase of platelets and intense erythro-leucoblastic activity, recognized by a great increase of immature granular cells and nucleated erythrocytes in the peripheral blood.

*Post-mortem examination.* Examination of the various organs revealed the characteristic changes resulting from prolonged and severe anaemia.

*The liver* weighed 2,460 grm. and showed no naked-eye evidence of cirrhosis. The liver cells proximal to the portal spaces were markedly atrophied and the sinusoids between the cells definitely widened. The cytoplasm was very granular and contained much haemosiderin. The cells in the central parts of the lobules formed a structureless homogeneous mass in which the nuclear staining was to a large extent lost. Reticulo-endothelial cells were prominent and showed marked phagocytosis of erythrocytes and pigment. No evidence of ectopic foci of blood regeneration was seen. A divergence of opinion existed among several pathologists to whom sections were submitted, as to whether the fibrous tissue was or was not increased in amount.

*The spleen* (removed at operation) weighed 815 gm. Several white infarcts and two haemorrhagic ones were seen.

Apart from some increase of fibrous tissue, the feature of particular interest was the proliferation in the pulp of cells of the reticulo-endothelial system. In many of these large cells haemosiderin and the 'ghosts' of phagocytosed erythrocytes could be seen. Typical fungus-like siderotic nodules, which occur so frequently in Banti's disease, were present. Myeloid metaplasia was a definite feature. The underlying pathological condition was described by several pathologists as being typical of reticulo-endotheliosis.

*The bone marrow.* A red but fluid marrow was present throughout all the marrow cavities in the body. Microscopical examination of stained films revealed no abnormality in the myeloid tissue but a marked reduction in the erythroblastic tissue.

*Summary.* A case of reticulo-endotheliosis with severe macrocytic anaemia which failed to respond to all forms of therapy, including splenectomy.

#### *Discussion*

*Macrocytic haemolytic anaemia. Group III (Cases 5, 6, 7, 8, 9).* Cases 6 and 7 illustrate extremely well how reliance on a colour index above unity, even when accompanied by achlorhydria, may lead to a faulty diagnosis. The need for repeated reticulocyte counts and estimations of bilirubin and urobilinogen in the blood and urine, respectively, are necessary for the purpose of distinguishing between macrocytic haemolytic anaemias and Addisonian pernicious anaemia. We are fortunate in being able to illustrate in Case 7 three haemolytic crises which occurred in 1935, during which a correct

diagnosis could have been made if the investigations mentioned above had been carried out. The failure of liver extract therapy and the success of splenectomy are well illustrated in both cases. Case 5 illustrates the result of failing to make a diagnosis of haemolytic anaemia at the correct time, when life could be saved by removal of the spleen. There was clear evidence from the history that the disease was present thirteen months before admission to hospital. The finding of a severe macrocytic anaemia with 40 per cent. of reticulocytes, together with a failure of the blood level to rise, was diagnostic of the condition. Additional points of interest in this case are, first, it serves as a good illustration of the dangers of transfusion in haemolytic anaemias in which the blood level is very low. The most careful cross-matching of the blood and the introduction of small quantities of blood, very slowly, are indicated in such cases. Secondly, pathological examination showed the typical picture of the changes in the spleen found in haemolytic anaemia, but, in addition, a well-marked coarse cirrhosis of the liver—a combination extremely rarely seen. It is difficult to supply an adequate explanation of the liver changes. It might be suggested that the liver damage was due to injury to the liver cells secondary to their continuous efforts in dealing with products of excessive red-cell destruction. If this were so, why is cirrhosis of the liver not more frequently found in familial acholuric jaundice, a disease in which increased blood destruction may continue throughout life? It is necessary to distinguish liver cirrhosis which is secondary to acholuric jaundice from the haemolytic jaundice described by various French workers (Mouisset, 1910; Chevallier, 1915), which occurs secondarily as a complication of cirrhosis of the liver and 'being in that case usually associated with infectious processes and the haemorrhagic diathesis' (Tileston, 1922).

Macrocytosis in haemolytic anaemias is certainly not due to lack of the anti-anaemic factor, since parenteral liver therapy is useless. Apparently prolonged and excessive erythroblastic activity results in the bone-marrow being filled with large primitive erythroblasts, the descendants of which have a mean diameter greater than normal. We are unable to explain the cause of these haemolytic anaemias, but we believe that these conditions can be acquired and are not necessarily always congenital, as is held by certain workers (Dawson, 1931). The north-east of Scotland has a static population which makes it easy to obtain a family history going back for two or more generations. We have repeatedly failed to obtain a history of a congenital element in many cases of haemolytic anaemia; nor have fragility tests carried out in the relatives given any additional information.

Case 8 is reported because in our experience we have never before been able to demonstrate in a typical haemolytic anaemia the presence of an infective agent. Those workers, who believe that infection is the primary aetiological factor in the haemolytic anaemias, base their views wholly on indirect evidence, namely, fever, rigors, sweating, tachycardia, and

leucocytosis. We are satisfied, however, that all such manifestations can result from excessive and rapid intravascular blood destruction. In parenthesis, we wish to say that we are doubtful whether there exists a type of acute haemolytic anaemia which can be separated from other haemolytic anaemias under the heading 'Lederer's Anaemia' (Lederer, 1925), since we know of nothing in the blood picture or clinical manifestations to justify this separation. The only valid reason for this subdivision appears to be the claim that blood transfusion produces a permanent cure in 'Lederer's Anaemia'. The word 'permanent' is deliberately used, since remarkable effects can be produced in many cases of acute haemolytic anaemia by blood transfusion, which appears to break the vicious circle in some way as yet not understood. The beneficial effects, however, are temporary, in our experience, since a relapse occurs within weeks or months if splenectomy is not undertaken. Information is urgently required about cases described as belonging to the group of 'Lederer's Anaemia' in regard to their late prognosis. It should be realized that although infection is not the cause of haemolytic anaemias, it may be the means of inducing a blood crisis in those with a haemolytic tendency. Thus the effect of infection was seen in Case 6, who, in May 1937, suffered from respiratory disease which was followed by a sharp fall in the blood level and a rise in the serum bilirubin and the reticulocyte count.

Case 8 appears to be unique also from a bacteriological standpoint, since Dr. John Smith, an acknowledged authority on the *Salmonella* group of organisms, and the Dublin strain in particular, informs us that he knows of no case of infection with this organism in which a haemolytic anaemia developed. We feel, therefore, that the patient, despite the absence of a history of previous haemolytic phenomena, was in reality a case of latent haemolytic anaemia precipitated into a blood crisis by a *Salmonella* infection most probably derived from contaminated milk.

We would draw attention to a point of great interest in Cases 6 and 8, viz. the presence of an increase of bilirubin and reticulocytes in the blood continuously for many months after splenectomy. Since these signs indicate haemolysis of erythrocytes by the reticulo-endothelial system, and since the spleen was removed, together with any spleniculi present, it must be assumed that excessive blood destruction is still proceeding in the liver and bone marrow, where the reticulo-endothelial cells are known to be present in large numbers.

Case 9 is an example of a rare condition, namely, reticulo-endotheliosis. When first seen the blood picture was indistinguishable from Addisonian pernicious anaemia, the raised reticulocyte count being attributed to liver extract therapy. Nevertheless the gross enlargement of the liver and spleen present from the beginning made us dubious of this diagnosis and caused us to inform the family doctor that the patient was suffering from a macrocytic anaemia due to some primary disease of the liver and spleen. These views were confirmed by the finding of a falling blood level despite the continuation of Anahaemin injections and by the presence of free hydrochloric acid in the

gastric contents. During the course of the disease the features described as 'leuco-erythroblastic' anaemia (Vaughan, 1936), developed, the principal causes of which, viz. deposits of malignant tissue in the bone marrow and osteosclerosis, were looked for and not found. Accordingly we classified the patient provisionally as belonging to the group of severe macrocytic anaemias accompanying liver disease, a view which was supported by the development of free fluid in the abdomen and the finding of a low serum protein. Professor Beattie, who conducted the post-mortem examination, is of opinion that gross damage to the liver existed, since sections showed the liver cells markedly degenerated and atrophied. The diagnosis of reticulo-endotheliosis is based principally on the histological changes in the spleen, and we are indebted to Professor McNee and Drs. McMichael and Janet Vaughan for their reports on the sections submitted to them. Apart from the hyperplasia of the reticulo-endothelial cells, and the presence of foci of myeloid metaplasia, we were greatly impressed with the remarkable degree of phagocytosis of red cells by large endothelial cells, and we wonder whether the severe anaemia and the raised serum bilirubin content could be explained by this destruction of erythrocytes. One must assume that the nucleated red cells in the circulation were coming from the metaplastic foci in liver and spleen rather than from the bone marrow, since examination of the bone marrow showed that erythroblastic activity was subnormal.

*Case 10.* A. S., male, aged 34. Occupation: woodcutter. Transferred from the venereal diseases ward of the Aberdeen Royal Infirmary to one of us (L.S.P.D.) on 27th March, 1935, because of severe anaemia.

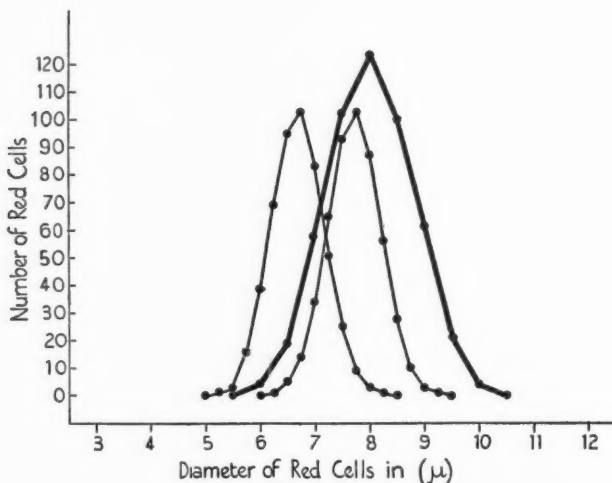
*History.* A reliable history was difficult to obtain owing to the very weak condition of the patient and to his subnormal intelligence. It appeared that he had been weak, easily tired, and made breathless for about a year, and these symptoms had increased rapidly during the previous two weeks. Five weeks earlier he developed gonorrhoea and was successfully treated for this in the venereal diseases department, first as an out-patient and then in the ward. The patient had at no time received injections of any arsenical preparation.

*Family history.* No history of anaemia or jaundice.

*Examination.* Patient was poorly nourished and showed extreme pallor without icterus. The teeth were badly decayed and the tongue was moist and furred. There was congenital ptosis of the right eyelid and a congenital deformity of both hands, resembling claw-hand. There was oedema of both legs and thighs and an area of deep cellulitis apparently going on to abscess formation on the outer side of each thigh. Over the right tibia there was a broken-down varicose ulcer. There was no urethral discharge. On admission the temperature was 102.6°. During his stay in the ward it was irregular, but never went higher than this. Examination of the cardiovascular system showed that the apex-beat was in the nipple line in the fourth left interspace. The heart sounds were very weak. The pulse-rate was 100, and the blood pressure 136/60. The chest showed an impaired percussion note and crepitations at both lung bases. The abdomen was distended and the umbilicus was flush with the surrounding skin. Several distended superficial veins were present, carrying blood from the umbilicus towards the thorax, flanks, and groins. Liver dullness was absent. The edge of the

spleen was just palpable. Shifting dullness in both flanks indicated the presence of free fluid. There was no tenderness or rigidity. Nothing of note was discovered on examination of the nervous system. The urine contained albumin and red-blood cells and pus. The benzidine test in the faeces was strongly positive.

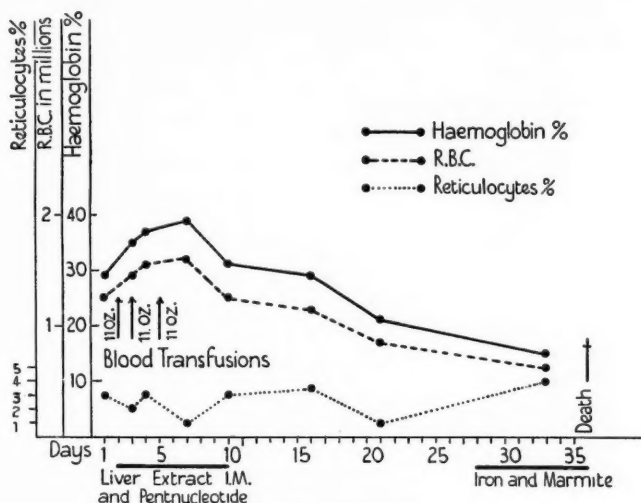
A diagnosis of atrophic cirrhosis of the liver was made on the basis of these findings.



CASE 10.

On 26th March blood examination showed: Hb. 29 per cent.; r.b.c. 1.28 millions; C.I. 1.16; mean diameter  $8.02 \mu$ ; w.b.c. 700; reticulocytes 3.2 per cent. The red cells were well stained, and showed macrocytosis. The cells lacked the oval shape and did not show the degree of anisocytosis and poikilocytosis which characterize pernicious anaemia of this severity (see Price-Jones curve). The platelets were very scanty. The few white cells seen in the stained film were all lymphocytes or mature polymorphs. The blood findings suggested a diagnosis of aplastic anaemia. The subsequent blood counts are shown in the chart. The patient was treated with liver extract, pentnucleotide, iron, arsenic, and marmite. Apart from slight improvements following blood transfusions, the Hb. level and red-cell count decreased. The white-cell count increased slowly, reaching a maximum of 2,800 per c.mm. on 27th April. The differential white-cell count at this time was: polymorphs 44 per cent.; lymphocytes 54 per cent.; eosinophils 2 per cent. On 29th March an abscess in the left leg was aspirated, 10 c.c. of pus giving a culture of *Staphylococcus aureus* were withdrawn. X-ray examination on 4th April showed a marked increase in the heart shadow, suggesting hydropericardium. The long bones revealed no abnormality except slight osteoporosis. On 22nd April an abscess in the right thigh was opened and packed. At this time the general condition of the patient was much worse. He became stuporose and frequently delirious. Diarrhoea and incontinence of faeces developed. The stools were fluid, dark green, and occasionally streaked with red blood. Death occurred on 2nd May.

A nurse who had attended him developed dysentery. Dysentery bacilli of the Sonne type were obtained from cultures made from her stools and also from the colon removed at autopsy from the patient.



CASE 10.

*Post-mortem examination 6½ hours after death:*

The body was that of an extremely emaciated man and skin haemorrhages were present on the anterior surface of the abdomen and thorax.

The pleural, pericardial, and abdominal cavities contained fluid, that in the pericardium being slightly blood-stained and containing flakes of fibrin, while that in the abdomen was bile-stained. The myocardium showed fatty change of the 'thrush-breast' variety. The foramen ovale was patent. The veins at the cardiac end of the oesophagus were distended.

The alimentary tract as a whole was oedematous, and in the ileum there were haemorrhagic ulcers. The colon throughout showed oedema and thickening and a nodular appearance suggesting chronic bacillary dysentery. The mucous membrane was necrotic and ulcerated in patches, and a marked fibrinous exudate was present over wide areas. Some of these ulcers, on microscopic examination, appeared to be of recent origin.

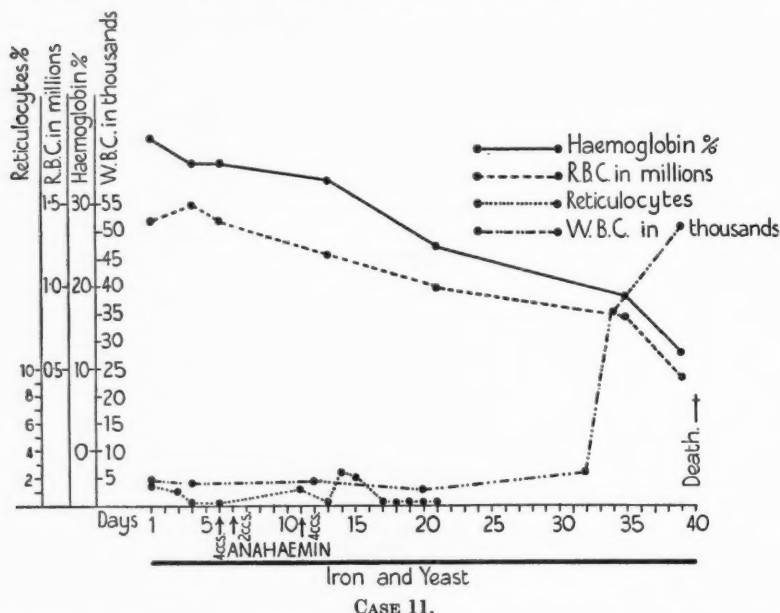
The liver showed a marked degree of portal cirrhosis. The right lobe was greatly reduced in size, while the left lobe was hypertrophied.

The spleen was enlarged, weighing 575 grm. Its consistence was firm and its substance was of a dark purple colour. Several infarcts were present, and scattered here and there were bright yellow siderotic nodules. Microscopic examination confirmed the presence of infarcts and siderotic nodules. The pulp was atrophic and the sinuses appeared to be widened and their walls a little thicker than normal. The pulp tissue contained very few erythrocytes. No phagocytosis was seen and the only iron pigment present was in the siderotic nodules. These appearances might be accounted for by the long-standing liver cirrhosis.

*Summary.* A case of macrocytic aplastic anaemia with liver cirrhosis and chronic bacillary dysentery.

*Case 11.* R.M., male, aged 57. Occupation: labourer—admitted to Aberdeen Royal Infirmary on 17.2.37, complaining of general weakness of three months' duration.

*History.* Three months before the patient had profuse epistaxis which



lasted for two hours. This was followed by progressive weakness and breathlessness on exertion. Nine weeks previously to admission these symptoms were so severe that he was compelled to stop work. Giddiness occurred frequently and there was a continual buzzing in the ears. There was slight loss of weight and appetite, but no abdominal pain or vomiting. For a few weeks before admission he took  $1\frac{1}{2}$  lb. of liver weekly.

*Previous history.* Seven years ago the patient suffered from weakness and 'bloodlessness', but was unable to give details of this illness.

*Family history.* Nothing of importance.

*Physical examination.* The patient was well nourished, but showed marked pallor without icterus. A few small shotty glands were palpable in the left posterior triangle of the neck and in the left axilla. There was no atrophy of the lingual papillae.

*Abdomen.* The lower level of liver dullness was 2 in. above the costal margin. There was no enlargement of the spleen.

*Cardiovascular system.* Blood pressure 162/74. There was no enlargement of the heart. A systolic murmur was present at all areas.

*Respiratory system.* Apart from crepitations at both lung bases nothing abnormal was noted.

*Nervous system.* The right knee-jerk was more active than the left. Ophthalmoscopic examination showed retinal haemorrhages and some pale exudates.

27.2.37: Blood examination: Hb. 38 per cent.; r.b.c. 1.4 millions; C.I. 1.36; reticulocytes 1.5 per cent.; w.b.c. 4,600. Examination of a

blood film showed that the red cells were macrocytic, but there was not the marked degree of anisocytosis and poikilocytosis characteristic of pernicious anaemia at a similar blood level. No nucleated red cells were seen. The platelets were scanty and were mostly single large forms. Apart from the presence of a leucopenia no information was obtained from the white cell picture other than the presence of moderate relative and absolute lymphocytosis with an occasional immature cell of the lymphocyte series. Icterus index 3. Laevulose tolerance test normal. Bromsulphthalein liver function test normal. Barium meal showed nothing abnormal. Blood urea 43 mg. per cent. Fractional test meal showed hyperacidity.

Owing to the resemblance of the blood picture to pernicious anaemia and the absence of data permitting a definite alternative diagnosis, the patient was treated by injections of Anahaemin (B.D.H.). In addition iron and yeast were given orally. No reticulocyte response occurred and the blood count slowly fell. On 20.3.37 total white cell and differential white cell counts were made before and after the subcutaneous injection of 15 minims of adrenaline. The white cell count before the injection was 3,000, of which 65 per cent. were mature lymphocytes and 5 per cent. immature lymphocytes. One half-hour after adrenaline injection the white cell count was 9,200, of which 6 per cent. were immature and 81 per cent. were mature lymphocytes.

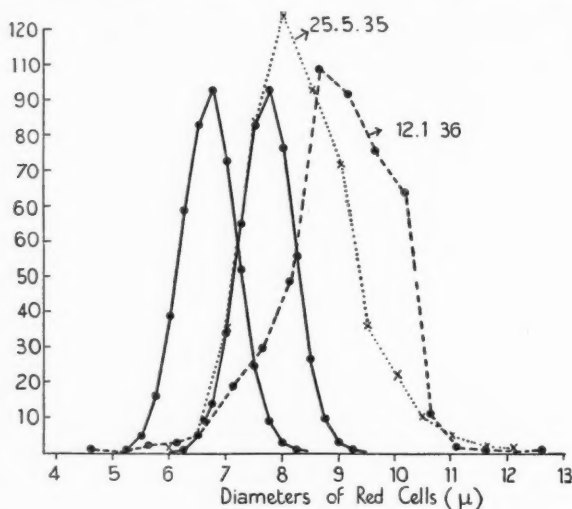
On 25.3.37 the sternum was trephined by Professor J. R. Learmonth and smears were made of the bone marrow. These showed that fully 90 per cent. of the bone marrow cells were lymphoblasts. A diagnosis of aleukaemic lymphoblastosis was therefore made. The blood level fell gradually and the patient died on 6.4.37. Shortly before death the blood count was: Hb. 12 per cent.; r.b.c. 470,000; C.I. 1.28. Four days before death the white cell count rose to 35,000 and increased to 51,800 shortly before death. The differential white cell count on the latter occasion was: lymphoblasts 58 per cent.; lymphocytes 21 per cent.; myelocytes 3 per cent.; metamyelocytes 2 per cent.; polymorphs 7 per cent.; monocytes 9 per cent. Unfortunately, permission for autopsy could not be obtained.

*Summary.* A case of aleukaemic lymphoblastosis with severe macrocytic anaemia, terminating with a frank lymphoblastic blood picture.

*Case 12.* A. F., male, aged 23. Occupation: valet. Admitted to the wards of Aberdeen Royal Infirmary under the care of one of us (L. S. P. D.) on 26th April, 1935, complaining of weakness, shortness of breath, and pain behind the knees of twenty months' duration.

*History.* In January 1933, the patient had an illness of short duration which was diagnosed as 'influenza'. Four or five weeks later he suffered a relapse, during which repeated and very severe epistaxis occurred. Following this he was fairly well, except that he complained of general lassitude, shortness of breath, and pain behind the knees, which had become severe by July 1933. His friends remarked on his yellow colour. Epistaxis occurred intermittently and was copious. In November 1933, he was admitted to St. George's Hospital, London. There a diagnosis of pernicious anaemia or aplastic anaemia was made and he was treated with iron, arsenic, injections of Campolon and Hepatex and by a series of ten blood-transfusions. A few of the blood examinations made at this time are contained in the chart. This treatment was ineffectual, apart from slight rises in the blood level, after the transfusions. In November 1934, he returned to Scotland and carried out his instructions by eating half a pound of liver daily. Two blood examinations which were done in Edinburgh at this time are included in the chart.

Although he had been able to walk about and take exercise, he thinks that his condition has not improved since the onset. Nevertheless it is noteworthy that in spite of a very low blood level he had been able to dance and to play tennis—a good illustration of the adaptation which may occur in a case of anaemia of great severity if its development is sufficiently slow.



CASE 12.

*Previous history.* Frequent sore throats. No other illnesses.

*Family history.* Father, mother, six brothers, and three sisters are all alive and well. One sister died of encephalitis lethargica in 1922. No history of anaemia or jaundice.

*Examination.* Height 5 ft. 9 in. Weight 10 st. 6 lb. Pallor was marked and the skin had a yellowish muddy appearance. There was no icterus and no oedema. There were two carious teeth; no mouth lesions or glossitis. The tonsils were enlarged, but no pus was expressible from the crypts. The nails were normal. Examination of the abdomen and respiratory, circulatory, and nervous systems was entirely negative. In particular it was noted that no glandular, splenic, or liver enlargement existed. The maximum temperature during his stay in the ward was 99° F. The stools contained no occult blood and were normal in other respects.

*Urine.* Urobilinogen negative. No albumen or bile. Blood urea 27 mg. per cent.

*Fractional test meal.* Fasting achlorhydria, hyperacidity in response to gruel meal reaching 50 units at 1½ hours. X-ray examination of long bones and mediastinum was negative. Blood Wassermann reaction negative. Icterus index 3. Van den Bergh reaction negative.

*Blood examination.* The blood count on admission was: Hb. 35 per cent.; r.b.c. 1.36 millions; C.I. 1.30; w.b.c. 2,660; reticulocytes 16.0 per cent. Cell volume index 1.16. The red cells appeared large, oval, and well stained. No nucleated red cells were seen. Differential count: polymorphs 43 per cent.; lymphocytes 54 per cent.; eosinophils 0; basophils 0; monocytes 3 per cent. Blood-platelets 45,000 per c.mm. Bleeding time 6 minutes.

Fragility test normal. The Price-Jones curve (25.5.35) (Fig. on p. 78) showed a shift to the right. Mean cell diameter  $8.34\mu$ . The absence of marked anisocytosis is noteworthy. On 10th May the sternum was trephined and part of the bone-marrow removed for examination. This showed a well-marked erythroblastic reaction. All types of nucleated red cells were present. The majority conformed to a cell-type between the megaloblast and normoblast, being intermediate in size and showing an open nuclear network with nodes of chromatin and a cytoplasm only partly haemoglobinized. Myelocytes and polymorphs were present in abundance. Later examination of marrow from the shaft of the tibia (15.7.35) showed pale and fatty marrow with no evidence of erythropoiesis or leucopoiesis. In the chart are shown representative blood counts. It is seen that a remarkably stationary blood level was maintained in spite of treatment by liver and liver extract, marmite, massive doses of iron, thyroid, adrenaline, prolan, and anterior pituitary extract, and in spite of a continued reticulocytosis. The leucopenia and low level of blood platelets also persisted, and the icterus index which was estimated on several occasions was always normal.

As a last resort it was decided to perform splenectomy. This was done by Professor J. R. Learmonth on 18th July, after a blood-transfusion. The spleen weighed 165 grm. The patient made a satisfactory recovery, but the blood picture was unaltered except for an increase in the white cells and platelets. Treatment with liver extract and iron was continued and the patient was discharged on 24.8.35, with a blood count of: Hb. 40 per cent.; r.b.c. 1.62 millions; C.I. 1.25; w.b.c. 5,400; reticulocytes 6.9 per cent., which was very similar to that on admission four months previously.

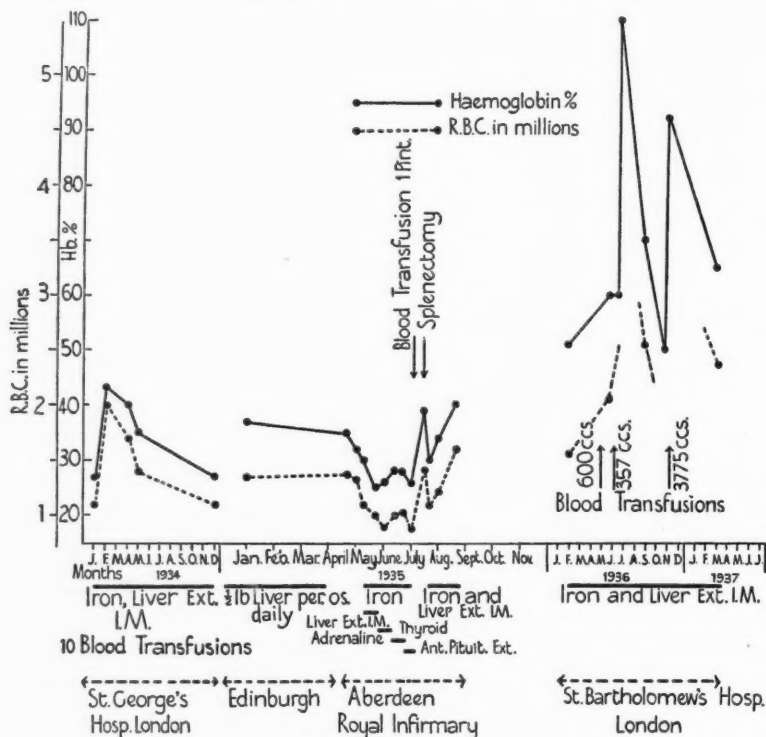
Despite the low Hb. level the patient again started work as a valet and was able to carry out his duties satisfactorily. As he was employed in London he was asked to report to Professor L. J. Witts of St. Bartholomew's Hospital, to whom we are indebted for the following information: On 5.2.36 the red-cells count was practically unaltered, but the colour index had increased to 1.65, a figure in keeping with the marked macrocytosis present in the films sent to us for examination. The increased degree of macrocytosis was confirmed by a Price-Jones curve which showed a mean diameter of  $9.36\mu$  (see p. 78). Polychromatic red cells were present in increased numbers and nine nucleated red-blood cells per 100 white-blood cells were counted. Anisocytosis was slight in degree and platelets were scanty.

The failure to improve on symptomatic treatment induced Professor Witts to give seven pints of blood intravenously by the continuous-drip method. As a result the Hb. rose to 110 per cent. and the patient's strength was markedly improved. Despite the continuous daily administration of iron and a hog's stomach preparation the blood level steadily fell, and three months after the transfusion a blood count made in Aberdeen showed Hb. 70 per cent.; r.b.c. 2.57 millions; C.I. 1.37; C.V.I. 1.44; reticulocytes 1.5 per cent.; w.b.c. 5,400. For the first time a raised icterus index, viz. 12, was found, with a faintly positive indirect reaction. This was assumed to be due to haemolysis of the transfused blood. The red-cell picture showed the presence of Howell-Jolly bodies in many corpuscles; two normoblasts per 100 w.b.c. were counted. The differential w.b.c. count showed a shift to the left in the granular series, with a decrease in the lymphocyte percentage.

Two months later another continuous-drip blood-transfusion of 3,775 c.c. was given at St. Bartholomew's Hospital, London. The Hb. at the end of the transfusion was 90 per cent. Since then 4 c.c. of Campolon have been injected weekly and iron has been taken periodically. Despite this treatment

the blood count had fallen on 10.3.37 to: Hb. 65 per cent.; r.b.c. 2.34 millions; C.I. 1.38. The patient continues to feel well and carries on his duties as a valet. Further massive blood-transfusions will be given as required.

Report on spleen removed at operation 18.7.35. The Malpighian corpuscles are well marked and have small but active germ centres. They



CASE 12.

are widely separated by an increase in the amount of pulp tissue, this increase being due to dilatation of the sinuses and a hyperplasia of the reticulum cells. Only small numbers of red-blood corpuscles are present, and there is no sign of increased phagocytosis or of excessive pigment deposition. The histological appearances are not diagnostic of any specific disease.

**Summary.** A case of severe macrocytic anaemia of unknown aetiology, which failed to respond to all forms of therapy, including splenectomy.

#### Discussion

**Macrocytic aplastic anaemia. Group IV (Cases 10, 11, 12).** The classical haematological features of aplastic anaemia were present in Case 10, viz. a marked reduction of erythrocytes, leucocytes, and platelets. Accompanying these changes were the characteristic clinical features, viz. severe

anaemia, haemorrhage, and sepsis. With regard to the aetiology of the anaemia, we would suggest the following explanation: chronic bacillary dysentery leading to absorption of toxic products into the portal vein, causing hepatitis and cirrhosis of the liver. It is impossible to state whether the same toxic products which damaged the liver damaged also the bone-marrow, or whether the aplasia was secondary to the liver damage. If the latter view is accepted, the finding of a macrocytic, as opposed to the customary normocytic picture in aplastic anaemia, could be explained.

Case 12 is, for the following reasons, one of the most remarkable cases we have had the opportunity of studying, firstly, because of the ability of the individual to work full time as a valet and enjoy social recreation, such as dancing, with a red-cell count which remained in the neighbourhood of 1 to  $1\frac{1}{2}$  millions for a period of more than two years; secondly, because of his failure to react to all forms of treatment, including splenectomy but excluding the temporary good effects of massive blood-transfusion, despite the fact that biopsy material removed from the sternum revealed a hyperplastic marrow; thirdly, because of our inability to demonstrate any cause of the anaemia. The history of severe nose-bleedings at the beginning, of his illness might be considered to be either the cause of the anaemia, or, alternatively, merely another symptom of the underlying condition. Fourthly, the diagnosis of the type of anaemia present is of great interest. The differential diagnosis lies between aplastic, achrestic, and haemolytic anaemia. In favour of the first are the following blood findings, viz. intense anaemia and considerable depression of leucoblastic and megakaryocytic activity. The presence of free hydrochloric acid in the stomach is against the diagnosis of Addisonian pernicious anaemia, and fails to help in the differentiation of the other three conditions. The absence of an increase in the serum bilirubin in the presence of a severe anaemia contra-indicates the diagnosis of a haemolytic anaemia or pernicious anaemia. The presence of a raised reticulocyte count on many occasions for long periods, with a stationary blood level, is in favour of haemolytic anaemia and is generally held as evidence against aplastic anaemia, but this view we feel requires further consideration. We believe that aplastic anaemia can occur under two conditions: (a) diffuse widespread bone-marrow aplasia, and (b) a patchy aplasia in which small portions of bone-marrow show signs of hyperplastic activity in an attempt to compensate for aplasia of large parts of the red bone-marrow. Such a condition was well described by Sheard (1924) in both aplastic and pernicious anaemia, in which areas of erythroblastic or megaloblastic proliferation were scattered throughout the bone-marrow.

Excessive erythroblastic activity in time leads to macrocytosis, provided that the building materials for red cells are present in ample quantities. As a result of the hyperplasia red-cell production is transferred from a normoblastic to an erythroblastic type, but not to megaloblastic production which occurs for totally different reasons which have already been described. A study of the graph of Case 12 indicates that it would be difficult to

distinguish the blood changes occurring in a case of aplastic anaemia with a patchy hyperplastic bone-marrow from a case of haemolytic anaemia, without data regarding urobilinogen excretion and the serum content of bilirubin. In a patchy aplastic anaemia the portions of remaining hyperplastic marrow attempt to supply the demands for erythrocytes by liberating prematurely into the circulation immature cells. The reason why the red-cell level does not increase despite the raised reticulocyte count is because the absolute number of cells turned into the circulation is so small. The diagnosis of diffuse aplastic anaemia was ruled out in this case by the finding of hyperplastic marrow in the sternum. In a case of haemolytic or hypochromic anaemia which had existed at the level of 1 million cells for a year or more, one would expect to find red marrow in the shaft of every long bone; but since a biopsy specimen removed from the tibia contained no erythroblastic cells, we believe that this case represents a type of aplastic anaemia in which the bone-marrow has been destroyed in all areas save a few patches in the flat bones.

The final differentiation between aplastic anaemia of the type described, and achrestic anaemia, must depend on a study of the marrow throughout the whole skeleton. We are without this information, since our patient is still alive; nor have we sufficient information in regard to achrestic anaemia, because Israëls and Wilkinson's observations (1936) were confined to the femur. The marked leucopenia and thrombocytopenia are in keeping with a diagnosis of aplastic anaemia, and the increase in the macrocytosis which occurred between September 1934 and March 1936 (see Price-Jones curves) suggests that the remaining erythroblastic tissue has become increasingly hyperplastic in an attempt to maintain the erythrocyte level. Many of the arguments used above are applicable to Case 2, since the patient has remained for approximately three years at a level of about 3 million red-blood cells, which we are unable to alter by any treatment excluding blood transfusion. The diagnosis lies between achrestic anaemia and hypoplasia of the bone-marrow.

Case 11 is included in the aplastic group, because it was finally determined that the intense anaemia, leucopenia, and thrombocytopenia were due to the crowding out of existence of the formative elements by primitive leucoblastic cells. Here, again, we believe that the high-colour index anaemia was due to excessive hyperplasia of the remaining erythroblastic elements, and not to a deficiency of the blood-maturing factor. The red-cell picture was in our experience indistinguishable from a case of pernicious anaemia in relapse, no matter what criterion was adopted. Finally, attention is drawn to the value of adrenaline injections and examination of bone-marrow obtained by sternal biopsy in establishing the diagnosis in aleukaemic lymphoblastosis. Such procedures are particularly indicated in cases of macrocytic anaemia with free hydrochloric acid in the gastric juice.

*Summary*

1. In a previous issue of this Journal a description was given by one of us of nine cases of macrocytic anaemia which were proved not to be pernicious anaemia. In this paper the clinical manifestations, haematological findings, and additional investigations of a further twelve cases are reported.

2. The cases have been divided into the following groups:

(a) Two cases illustrating transference from a hypochromic microcytic anaemia to a hyperchromic macrocytic anaemia.

(b) Two cases of macrocytic anaemia due to liver disease.

(c) Five cases of haemolytic anaemia, one of which was caused by a *Salmonella* infection (Dublin strain) and another proved to be a case of reticulo-endotheliosis.

(d) Three cases of aplastic anaemia of various types.

3. A discussion is given of the mechanisms by which macrocytosis may arise.

4. Attention is directed to the importance of correct diagnosis, and methods are described for the achievement of this purpose, since the prognosis and treatment of this group of macrocytic anaemias is entirely different from the megalocytic anaemias resulting from defective production or absorption of the anti-pernicious anaemia factor.

We are indebted to Dr. W. M. Davidson, Lecturer in Pathology, University of Aberdeen, for the pathological reports given in this paper, and to Professors Beattie and McNee and Drs. McMichael and Janet Vaughan for their help in the case of reticulo-endotheliosis.

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## THE RADIOLOGY OF PULMONARY INFARCTION<sup>1</sup>

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With Plates 3 to 6

THE present investigation was undertaken with the object of determining the X-ray appearances produced by infarction of the lung whether due to embolism or to thrombosis in pulmonary blood-vessels; it was also hoped to discover in what way the shadows produced in the lung by these lesions differed from those well recognized as due to such states as pneumonitis, tuberculosis, pleurisy, and pleural effusion.

There is not an extensive literature regarding the radiology of pulmonary infarction. Kohlmann (1924) remarked that X-rays showed infarction to occur most commonly in the middle and lower lobes of the right lung; he considered that radiological examination might help to clinch the diagnosis in certain cases of pulmonary infarction in which clinical evidence was inconclusive. Wessler and Jaches (1923) observed that only large infarcts gave shadows on the film, while autopsy often revealed small infarcts not shown by radiological examination during life. They found that large shadows of triangular shape with the base towards the axilla were the most characteristic. Surrounding inflammation might make such areas of density indistinguishable from those produced by pneumonic consolidation. These observers remarked that an embolic origin must not be assumed for all shadows found in the lung in the course of heart disease: for example, true pneumonia might be due to rheumatic infection, or to some other organism related to chronic endocarditis. Sante (1930) also found that no radiological evidence might be discovered even though acute and typical symptoms had been present, and the existence of infarction proved at autopsy; if infection were superadded then radiological signs were more likely to be found. Like Wessler and Jaches he described areas of increased density, often triangular in shape with the base at the periphery of the lung. The lower border of the upper lobe was found to be a common situation. Kirklin and Faust (1930) made a clinical and radiological study of 25 cases of pulmonary infarction; the diagnosis in eight of them was confirmed at necropsy. They found abnormal shadows in the X-ray in every case in which physical signs were present, and in some of those in which signs were indefinite. The base of the right lung was involved far more commonly than any other part. They concluded that although at times it was not

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possible to make a diagnosis of pulmonary infarction from radiograms alone, radiology was often a valuable supplement to clinical methods. In 1931, Sergeant, Bordet, Durand, and Couvreur included one radiogram of a pulmonary infarction in their 'Exploration Radiologique de L'Appareil Respiratoire'. This X-ray showed a small rounded shadow in the right mid-zone associated with clouding at the base. The authors commented on the fact that such a shadow of related effusion explained the rarity of well-defined shadows in films of pulmonary infarction. Kohler (1935) observed that the lower and middle zones of the lung at their outer margins were the regions most often involved. If the axis of the infarction were at right angles to the rays then a sharp outline might be seen and the expected triangular shadow produced; on the other hand, if the axis were parallel to the rays then a circular or oval shadow would appear and this might be erroneously interpreted as due to tumour, abscess, gumma, interlobar effusion, central pneumonia, actinomycosis, or echinococcus. Golden (1936) in his treatise on radiological diagnosis made no direct reference to pulmonary infarction, but referred to a condition of 'aputrid necrosis' under the heading of pneumonia. He stated that such a condition, accompanied by X-ray appearances of density and cavity formation, was due to pulmonary infarction; this disease might heal spontaneously, but it might cause perforation of the pleurae and consequent pyopneumothorax. Kerley (1936) has made repeated X-rays in some cases and has recorded rapid clearing of the shadows in the lung fields.

#### *Clinical Material and Method of Investigation*

The present series comprises thirteen patients, in all of whom the diagnosis of pulmonary infarction was undoubted. With the exception of one or two films which were taken prior to the onset of infarction, and one or two during the very late stages of healing, all the X-rays were taken by portable apparatus with patients well propped up in bed in the position of greatest comfort. It was not found that the procedure necessary to secure these pictures disturbed the patients or aggravated the condition in any way. Thirty films were thus obtained, the number in each case varying from one to five; in the larger series the films were taken at intervals, increasing from a few days to several weeks. Seven of the thirteen patients died in the course of the acute illness or afterwards; in each case a necropsy was obtained confirming the clinical diagnosis.

#### *Radiological Appearances in Pulmonary Infarction*

No complete classification of radiological findings in pulmonary infarction is yet possible. Until larger numbers of investigated cases have been published it cannot even be said that every type of shadow is known, and still less the relative frequency with which these various shadows occur.

The following groups have been put together as a broad outline probably covering the principal groups of X-ray appearances:

(i) *Hazy horizontal clouding at the base.* The development of hazy density at the base is a frequent finding in films taken within a day or two of pulmonary infarction. It is perhaps most likely to be found when the situation of pleural pain is low in the axilla or of diaphragmatic distribution. The clean outline of the costophrenic sinus will be hidden and the dome of the diaphragm will be partly or completely obscured. The shadow may be of a uniform milky haziness blending with normal lung shadows as it extends upwards, or it may show ill-defined lobulations. If the former, it may suggest a small pleural effusion except that the characteristic concave upper border with density highest in the axilla is not seen. If lobulated, the shadow may simulate that of influenzal pneumonitis. The following is an illustrative case:

A girl, aged 17, was admitted to hospital with heart disease of most unusual type for the age: mitral stenosis, hypertension and arteriosclerosis, cardiac enlargement. Plate 3, Fig. 1 (20.xi.35), shows the telerradiogram of the heart some days prior to admission. Nine days after admission the patient complained of pain in the right axilla, coughed up about two drachms of blood, and developed a temperature of 100° F.: pleural friction was heard on the same day, and on the next dullness and tubular breath sounds were present. Plate 3, Fig. 2 (6.xii.35), shows basal shadowing two days after onset. Necropsy (8.xii.35) showed a diffuse haemorrhagic infarct in right lower zone and a pleural effusion; no thrombi in the chambers of the heart; mitral stenosis of moderate degree; one organizing infarct, and one more recent, in the heart muscle at the apex; aorta small and moderately atheromatous.

(ii) *Shadows suggesting pleural effusion.* It is well recognized that pleural effusion may follow infarction of the lung, and shadows suggesting pleural effusion may be due actually to this, even though pulmonary infarction be the underlying cause. It has several times been found that localized density due to infarct develops into a larger shadow showing the characters of that due to effusion. Serial radiograms may, therefore, assist the differentiation. The presence of a fairly well-defined edge near the limit of density may or may not help, since in pleural effusion of, for example, tuberculous origin the lung-fluid interface may show as a clear edge through a milky density. Such a margin will ordinarily be curved with the concavity directed upward and inward. If a margin is seen, perhaps the convexity pointing upward and inward, the likelihood of its representing the edge of a pulmonary infarction would become greater. But it is important to realize that shadows representing effusion may conceal an underlying pulmonary infarction as in the following instance:

A woman, aged 74, had been treated for varicose veins by injections. Phlebitis developed and subsequently haemoptysis with signs of circulatory embarrassment. Pulmonary embolism was diagnosed. The patient was seen again after sixteen days, signs of fluid at the left base then being found. The X-ray in Plate 3, Fig. 3, shows the shift of heart and mediastinum to

the right and extensive density covering about three-quarters of the left lung field: appearance typical of effusion. An ill-defined margin is seen passing upward and outward just above the level of the angle of the scapula with convexity directed upwards: possibly the margin of the infarcted zone. Aspiration of 30 oz. of fluid from the left base relieved the respiratory and circulatory embarrassment and the patient made an uneventful recovery.

(iii) *Shadowing of roughly circular form suggesting lung abscess.* If the long axis of the obstructed vessel and the resultant infarct is at right angles to the X-rays, a sharply outlined triangular shadow may be seen; while if the axis is parallel to the rays then a circular or oval shadow may be produced. This may simulate the appearances of a lung abscess or interlobar effusion, as Kohler (1935) has mentioned. The differentiation may be most difficult if the shadow lies towards the central part of the lung. This problem is well illustrated in the following case record:

A man, aged 40, was admitted four and a half weeks after the crisis of an illness diagnosed as pneumonia. Four days after the crisis repeated rigors had developed, but these had ceased ten days before admission. Clinical and bronchoscopic investigation suggested a diagnosis of interstitial abscess in lung (Plate 3, Fig. 4). The patient died five days after admission. Necropsy showed vegetations on the tricuspid valve; death was due to bacterial endocarditis of this valve, probably pneumococcal. The right lower lobe contained a zone of infarction in a situation corresponding to the shadow in the film; infarcts, presumably developed subsequently to the radiogram, were also found in the right middle and left lower lobes.

(iv) *Density of part of one lobe with cavity formation.* Sometimes the opacity due to infarction occupies a position in the region of the middle zone of the lung. It may be a wedge-shaped shadow at the periphery of the lung field with the apex directed downward and the lower border obviously formed by the lower boundary of the upper lobe of the lung. In other examples the density may occupy the whole of one lobe: this is well seen in Plate 6, Fig. 13, where the right middle lobe is involved and the interface between this and the upper forms the horizontal upper border of the shadow. An appearance suggestive of a fluid level is thereby produced.

When infarction involves a large tract of lung, it is not surprising that colliquative necrosis may set in with the formation of a cavity. Golden (1936) has referred to this process under the term 'aputrid necrosis'. The formation of a zone of softening or of a cavity causes a central clearing in the density of the infarct shadow. If the liquefaction takes place near an interlobar septum, successive films may show an increasing bulge at the margin of the opacity, as in Plate 6, Figs. 14 and 15. Although pathological events of this kind render the outlook more serious, recovery may follow, as in the patient already mentioned. In this instance a film taken eleven weeks after the onset showed a horizontal fibrous scar as a relic of the recent infarct (Plate 6, Fig. 16). Comparable, though more advanced, changes took place in the following case:

A woman, aged 59, was admitted on account of gall-stones and biliary colic. The patient had mitral stenosis and aortic incompetence with general cardiac

enlargement (Plate 4, Fig. 5). Auricular fibrillation was present. Although she was an unsuitable subject for a major operation, this was being considered, as the recurring colic could not be checked by medical measures and rendered life intolerable. After rest and stabilization by digoxin, cholecystectomy was performed; recovery was uninterrupted for five days, when pain suddenly developed at the right base with fever, cough, and haemoptysis. A film taken six days after the onset showed the horizontal clouding already mentioned (*vide supra*) (Plate 4, Fig. 6). Seventeen days later the pain had taken a position higher on the right side of the chest. Signs of pleurisy and excavation of lung were found. Plate 4, Fig. 7, shows the radiological appearances, an extension of the previous basal shadow suggesting pleural effusion and a new area of density in the upper zone of the lung. Eleven days later the X-ray (Plate 4, Fig. 8) showed undoubted evidence of a large cavity in the upper half of the lung: note horizontal lower border of this shadow (junction of upper and middle lobes), also considerable clearing at the base. Necropsy revealed an infarct of triangular shape at the right base with no cavity; a large cavity of the size of a lemon was found in the upper zone, with necrosis and suppuration. There were plugs of ante-mortem thrombus in those branches of the pulmonary artery related to the two infarctions. The heart weighed 500 grm., mitral stenosis and aortic valve disease being present. The chambers of the heart contained no thrombi, but ante-mortem thrombi, probably the source of pulmonary emboli, were discovered in the veins in the pelvis.

(v) *Radiological appearances of basal collapse of lung.* Hazy density obscuring the base of the lung may, as it clears, disclose the dome of the diaphragm in an abnormally elevated position. It may be noticed, also, that the initial film shows the heart drawn to the side of the lesion and gradually regaining the normal position subsequently. The later films taken during resolution of the pulmonary lesion will show the interlobar septum in the normal position, while the rounded contour of the diaphragm has become straightened into a horizontal line. The outline of the diaphragm scarcely regains its normal definition, while the costophrenic sinus remains obliterated. Pulmonary changes showing radiological appearances of this kind may result either from pulmonary embolism or from primary thrombosis of pulmonary vessels. Sometimes the course of the illness is prolonged, the signs at the affected base alternately clearing up and reappearing. Effusions, usually of small bulk, may collect and be aspirated only to gather again. The shadows at the base of the lung will therefore show corresponding fluctuations of extent and opacity.

A woman, aged 53, with high blood-pressure, had a femoral thrombosis, and twelve days later pleural pain in the right axilla, associated with palpitation and severe respiratory distress. Dullness on percussion and weak breath sounds were present at the right base; Plate 5, Fig. 9, shows the X-ray appearance two weeks after the onset of the chest symptoms. For the following three months the patient remained ill with irregular fever. At the right base the signs fluctuated, sometimes suggesting effusion and at others progressive resolution. One or two further bouts of pleural pain corresponded with the periods of pyrexia. The film reproduced in Plate 5, Fig. 10, shows the final radiological appearance of the affected lung not long before

discharge and twelve weeks after the initial film: note the high position of the diaphragm, its relatively obscure outline, and the obliterated costophrenic sinus; also the scarring in the lung. From the normal position of the interlobar septum it is clear that the lower lobe of the right lung has undergone partial collapse.

(vi) *Linear shadows.* Dense linear shadows, suggesting the presence of a fibrous scar in the lung, are common radiological end results of pulmonary infarction. The cleanest linear forms are most likely to be seen at an interlobar septum as in Plate 6, Fig 16, already noted. Linear shadows, less well defined, are at times found at an earlier stage in pulmonary infarction. They may be seen at the base of the lung, perhaps an inch above the dome of the diaphragm, in a film taken for investigation of pleural pain developing a week or ten days after an operation. Such shadows, although not conspicuous, are quite distinct from the normal lung markings, and when they are found on the side corresponding to recent pleural pain, it may be conjectured whether they represent the opacity of a thrombosed blood-vessel or the consequent changes in the neighbouring lung. An example of an early linear shadow is given in the following case record:

A man, aged 60, was operated upon for stone in the bladder by suprapubic lithotomy. Ten days after the operation he was suddenly seized with catching pain at the lower part of the left axilla. This pain subsided in the course of two or three days, but a week after the onset some clots of dark blood were coughed up. The film shown in Plate 5, Fig. 11, was taken eight days after the onset; note the slight streaky density at the left base just above the diaphragm.

#### *Synopses of Additional Cases.*

1. A woman, aged 57, was admitted to hospital with right nephrolithiasis and *B. coli* infection. A pyelo-lithotomy was performed. Seven days later she developed severe pleural pain in the left axilla; pleural friction was heard. X-ray on the day of onset showed opacity filling the left costophrenic sinus and obscuring, though not obliterating, the outline of the diaphragm. Physical signs suggested subsequently the presence of a small effusion, but no indication for aspiration arose. The patient made a recovery that was otherwise uneventful and the signs in the lung disappeared.

2. A youth, aged 16, had acute rheumatism early in 1930, and complained afterwards of pain in the chest and shortness of breath. On 1st July, 1930, he was admitted to hospital with a history of two weeks' cough and slight haemoptysis three days previously. Examination disclosed mitral stenosis with normal rhythm; at the left base there was dullness on percussion, the air entry was poor, and pleural friction could be heard. Pulmonary infarction was diagnosed, and an X-ray taken on the day of admission showed clouding suggesting consolidation at the left base; the horizontal upper limit of this density was ill defined, and the opacity obscured the dome of the diaphragm and the costophrenic sinus. Three and a half years after recovery another X-ray showed the lungs to be quite normal and there was no trace of residual pleural thickening.

3. A man, aged 58, began to notice dyspnoea on exertion early in November 1934. After a fortnight he had a sudden onset of tightness in the epigastrium

while walking uphill, and became extremely short of breath. After a week or two, about the middle of December, he had to take to bed with congestive heart failure with oedema. The heart was grossly enlarged and the blood pressure 130/105. A diagnosis of recent cardiac infarction was made, and confirmed by successive electrocardiograms. He was admitted to hospital in failure, and within three days developed symptoms and signs indicating infarction in the right mid-zone. X-ray at this time showed opacity of the right middle lobe (Plate 6, Fig. 13). His condition gradually improved and successive X-rays showed liquefaction taking place in the infarct close to the interlobar septum (Plate 6, Figs. 14 and 15). A final film taken eleven weeks after the onset showed only a horizontal fibrous scar near the interlobar septum (Plate 6, Fig. 16). This patient became fairly well again and was discharged from hospital at the end of March 1935. After three months he became ill again and died. Necropsy confirmed the diagnosis of cardiac infarction; the right auricle contained thrombi, the probable source of the infarct in the right lung.

4. A woman, aged 48, had suffered from diabetes for ten years, and had been under treatment by diet and insulin. In November 1935 she developed a cough, and after a month pain at the left base with haemoptysis. When examined a fortnight later the following diagnosis was made: diabetes, hypertension (215/110), arteriosclerosis, cardiac enlargement, chronic bronchitis, pulmonary infarction at the left base. X-ray at this time confirmed the presence of gross cardiac enlargement and showed clouding at the left base suggesting effusion. Aspiration a week later brought 1 oz. of sterile fluid. Successive X-rays showed progressive clearing at the base, the dome of the diaphragm gradually becoming visible and later clearly demarcated. Although the patient made a good recovery from this illness she succumbed two months later to another infarction, this time at the right base. Necropsy was not obtainable.

5. A woman, aged 59, had been getting a little short-winded for a year or two. She awoke one night with a sensation of heaviness and oppression in the chest which later became a serious distress. These symptoms eased off after five hours; she stayed in bed but became feverish. Complete irregularity of the pulse was found at this time, but on admission to hospital the following day, the pulse was regular again. Signs of congestive failure were present. Signs at the left base suggested consolidation and probable small effusion. Diagnosis: hypertension and arteriosclerosis, cardiac enlargement, infarction of the left lung. X-ray five days after the onset of the illness showed dense horizontal clouding at the left base, obscuring the dome of the diaphragm and most of the outline of the left ventricle; also considerable enlargement of the heart and aorta. The illness pursued a fluctuant course with remissions followed by recrudescences of fever. Small quantities of sterile fluid collected at the left base and 4 oz. were aspirated on each of two occasions. Successive X-ray films showed variations in the extent of density at the left base, but ultimately, fourteen weeks after the onset, the opacity had largely cleared away. The patient made a satisfactory recovery from this illness.

6. A man, aged 49, had been getting short of breath for two years. Early in January 1936 the dyspnoea increased and a cough developed. After two or three days the sputum became stained with bright blood and the patient complained of sternal pain. He was admitted to hospital in this condition. Examination disclosed signs of congestive heart failure, with pulmonary oedema and a small effusion at the left base. X-ray on this day confirmed the clinical findings. These signs gradually cleared and the

general condition improved until ten days later symptoms and signs of infarction and effusion developed at the right base. The patient's condition deteriorated and he died a fortnight after the onset of the second infarction. Necropsy confirmed the presence of bilateral effusions and congestion of lungs with infarctions at the bases.

7. A man, aged 65, sustained a crushing injury to the leg at his work. About a week later, while he was in bed on account of this injury, there was a sudden onset of severe pain in the left axilla. Breathing or coughing made the pain worse and within a day or two he coughed up blood; the sputum continued stained for more than a week, and during this time he was feverish. He recovered from this illness and was about again five weeks after the accident when an exactly similar pain came on in the right axilla; the cough, fever, and haemoptysis returned and the patient returned to bed for another five weeks. He was the subject of arteriosclerosis, but had no other cardio-vascular disease. An X-ray was taken four months after recovery from the second bout of illness; it showed rather dense linear shadows at the right base just above the dome of the diaphragm (Plate 6, Fig. 12).

#### *Summary.*

1. Radiograms of the lungs were taken in thirteen patients suffering from pulmonary infarction, and in most of them serial films were obtained at intervals of days or weeks. In others it happened that a film of the thorax had been taken prior to the onset of infarction. Seven of the thirteen patients died in the course of the illness or afterwards. In all the fatal cases confirmatory necropsies were obtained.

2. The radiological features of pulmonary infarction were classified as follows:

- (i) Vague clouding at the base of the lung, obscuring the costophrenic sinus, and suggesting basal pneumonitis of influenzal type.
- (ii) Shadows indicating an early effusion either concealing a very recent infarct or being superimposed later on obvious intra-pulmonary shadows.
- (iii) Localized shadowing not unlike that of lung abscess.
- (iv) Density of greater or less extent, sometimes developing appearances indicating cavity formation, and consequently even suggesting pulmonary tuberculosis. Triangular or wedge-shaped shadows were only occasionally seen.
- (v) Shadows at one base with ultimate elevation of the diaphragm indicating partial basal collapse.
- (vi) Linear shadows representing scars of past healed infarcts, or if found soon after the onset, possibly representing changes due to thrombus formation.

For valuable criticism and for permission to study one patient under his care I am indebted to Dr. W. Burton Wood, Physician to the London Chest Hospital. For access to one patient under his care I have to thank Mr. E. A. Crook, Surgeon with Charge of Out-patients, Charing Cross Hospital. For permission to reproduce films I am grateful to Dr. Russell Reynolds, Physician in Charge of the X-ray Department, Charing Cross Hospital, and to Dr. Franklin Wood, Radiologist to the London Chest Hospital.

## DESCRIPTION OF PLATES

PLATE 3, FIG. 1. Female, aged 17. Mitral stenosis, cardiac enlargement and infarction, precocious arteriosclerosis and hypertension; before pulmonary infarction.

FIG. 2. Same patient. Film taken two days after onset of pulmonary infarction at right base, and showing hazy clouding at right base. Necropsy control.

FIG. 3. Pulmonary embolism following injection treatment of varicose veins. Film shows left-sided effusion and ill-defined margin of density with convexity upwards: possibly margin of infarct. Recovery followed aspiration of 30 oz. fluid.

FIG. 4. Pneumococcal infective endocarditis of tricuspid valve. Zone of density at right base suggesting abscess. Necropsy proved shadow to be due to pulmonary embolism.

PLATE 4, FIG. 5. Mitral and aortic valve disease; auricular fibrillation; cholelithiasis necessitating operation.

FIG. 6. Same patient. Right basal infarction occurred five days after operation. Film shows basal density six days after onset.

FIG. 7. Same patient, 23 days after onset of pulmonary infarction. Increased density at right base. New density with suggestion of cavity formation in right upper zone.

FIG. 8. Same patient, 34 days after onset of pulmonary infarction. Basal density has cleared. Extending colliquative necrosis in upper zone. Necropsy control.

PLATE 5, FIG. 9. Femoral thrombosis followed by pulmonary embolism. Film taken two weeks after onset of infarction shows clouding at right base with elevation of diaphragm due to partial collapse of lower lobe.

FIG. 10. Same patient. Film twelve weeks later. Diaphragm still high; costophrenic sinus obliterated. Note interlobar septum in normal position in this and previous film.

FIG. 11. Left basal infarct following supra-pubic lithotomy. Film taken eight days after onset. Linear density shown above left dome of the diaphragm.

FIG. 12. Arteriosclerosis. Right basal infarction following injury to leg. Film taken four months later, showing linear density above right dome of diaphragm.

PLATE 6, FIG. 13. Coronary thrombosis. Pulmonary infarction in right middle lobe; film taken 24 hours after onset. Note appearance suggesting fluid level (actually interface between middle and upper lobes).

FIG. 14. Same patient. Nine days after onset.

FIG. 15. Same patient. Twenty-one days after onset. This film and the previous one show local reduction in density below the interlobar septum which bulges upward at this point. Probable colliquative necrosis.

FIG. 16. Same patient. Convalescent, 11 weeks after onset. Film shows residual horizontal linear scar at outer portion of septum between middle and upper lobes. Necropsy control three months later: cardiac infarction and thrombi in right auricle.

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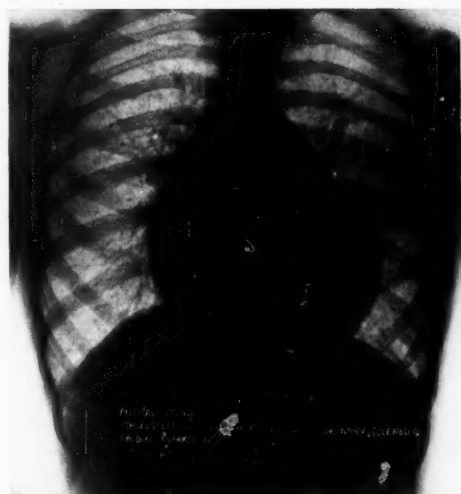


FIG. 1

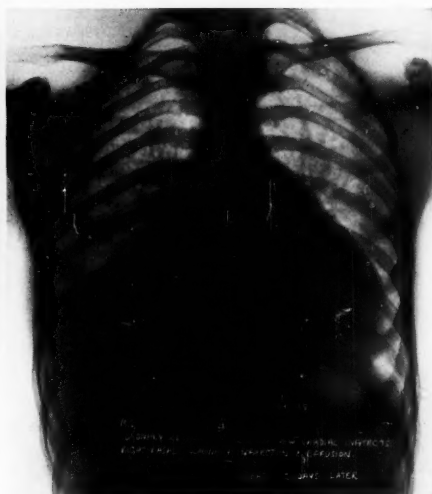


FIG. 2

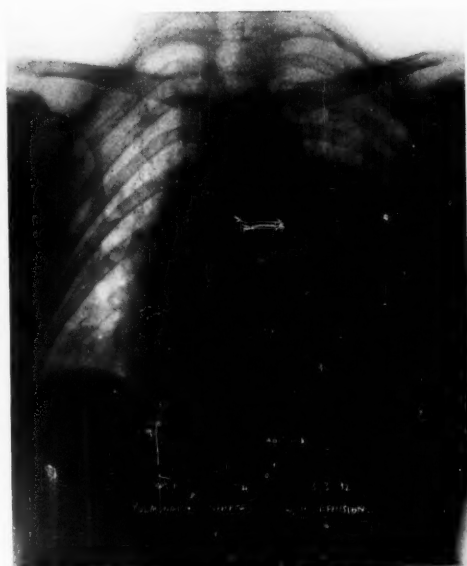


FIG. 3

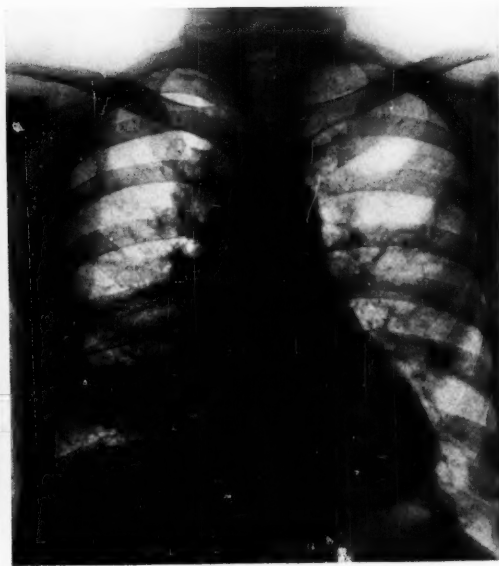


FIG. 4





FIG. 5

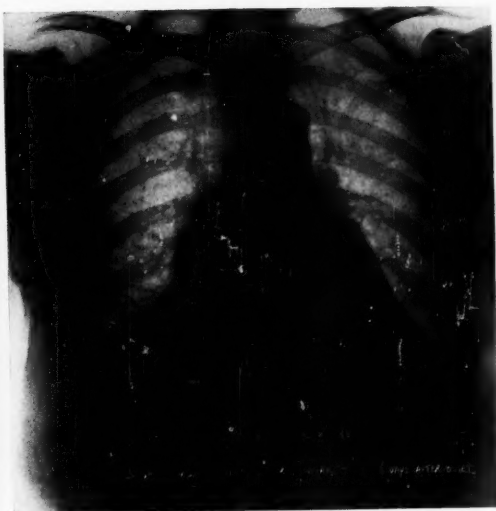


FIG. 6



FIG. 7

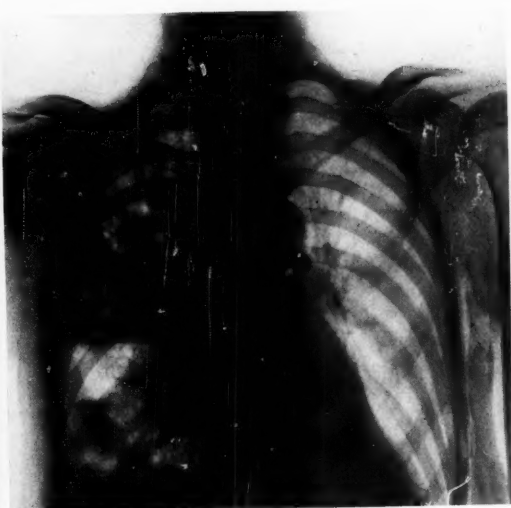


FIG. 8



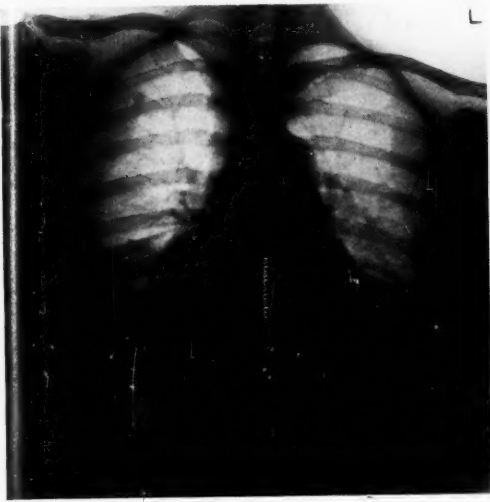


FIG. 9

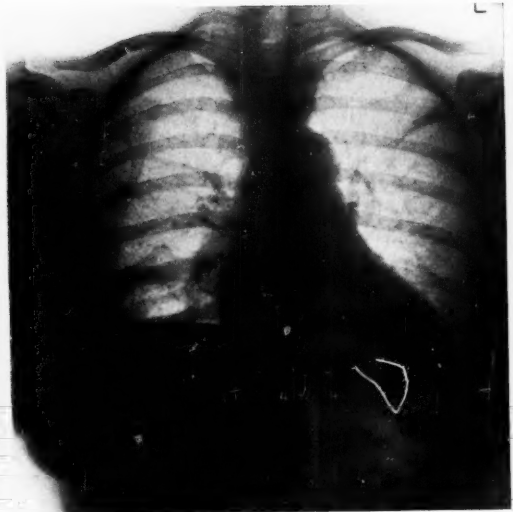


FIG. 10

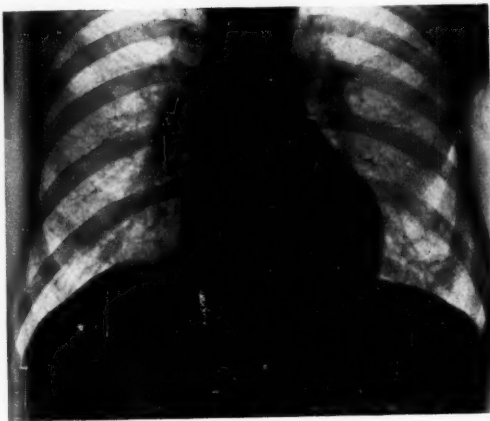


FIG. 11

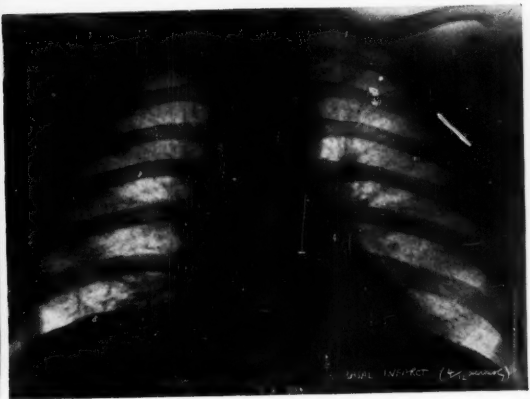


FIG. 12



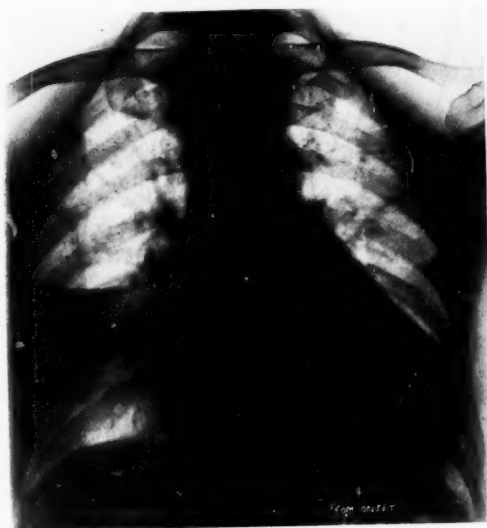


FIG. 13

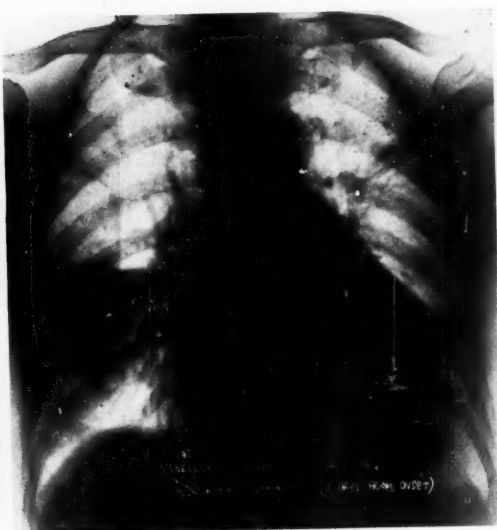


FIG. 14

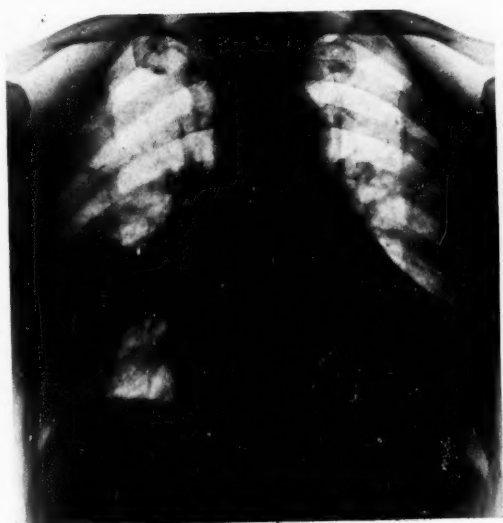


FIG. 15

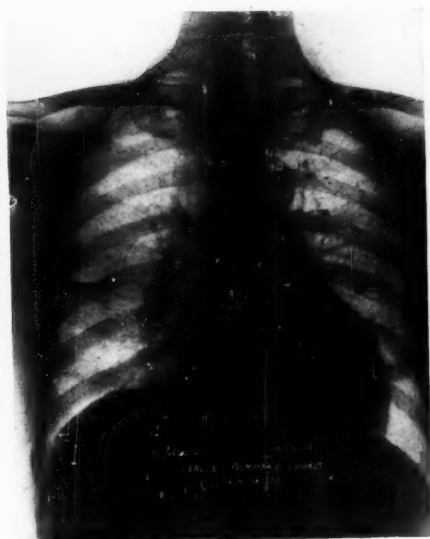


FIG. 16



## THE MARCHIAFAVA-MICHELI SYNDROME OF NOCTURNAL HAEMOGLOBINURIA WITH HAEMOLYTIC ANAEMIA<sup>1</sup>

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With Plates 7 and 8

THE syndrome of paroxysmal nocturnal haemoglobinuria with haemolytic anaemia was recorded first by Marchiafava and Nazari in 1911, and during the last quarter century some twenty-eight examples have been published. Micheli's (1931) paper, in which all published cases were reviewed and another example recorded, placed the condition on a firm clinical and pathological basis; in recognition of this fact Rosenthal (1932) suggested the eponym 'Haemoglobinuria recurrens vel nocturna cum anaemia haemolytica (type Marchiafava-Micheli).' The clinical aspects of this syndrome have recently been reviewed by Rosenthal (1932), Witts (1936), and Hamburger and Bernstein (1936). We have felt it unnecessary to repeat this in view of the adequacy of these accounts, but we now place on record two cases, carefully studied in life, in which full post-mortem examinations were made. The pathological aspects of the disease have attracted less attention than the clinical, and where autopsies are reported the details are often scanty. We have therefore considered the morbid anatomical and histological changes in fuller detail and discussed their relation to the disease-process, reviewing the pathological findings in other recorded cases.

### *Case Reports*

*Case 1.* Mrs. M. B., a housewife, aged 52 years.

Admitted to St Bartholomew's Hospital on 19th May, 1936, complaining of passing 'dark water'.

*History.* For the past four or five years she had had attacks in which she had passed dark urine. Each attack lasted from one to five days and there were periods of weeks to months between the bouts. They tended to occur when she had had a mild infection such as a cold in the head or a sore throat, and she had been told that her skin took on a yellow colour during the attacks. The attacks were not induced by low temperatures and were not accompanied by shivering, prostration, or cramps, nor indeed by any symptoms apart from the dark brown discoloration of the urine. She had had no symptoms suggestive of Raynaud's phenomena.

<sup>1</sup> Received September 14, 1937.

Recently she had had attacks of epigastric pain an hour after food radiating to the back and occasionally terminating in vomiting. She had noticed that she tended to bruise easily and thought that she had lost flesh in the past few months.

*Past history.* Two operations for the cure of a left inguinal hernia and one for uterine prolapse had been performed over twenty years ago. Thirteen years previously the uterus had been curetted, and six years ago a further curettage had been followed by insertion of radium and an anterior and posterior colpo-perineorrhaphy. Apart from these surgical procedures she had always had good health.

*Family history.* She came of sound stock and was married, with two healthy children. No similar disorder had occurred in her family. No relatives had suffered from jaundice or anaemia.

*Physical examination.* She was a pale, well nourished woman of sallow complexion. There was no icterus; a few soft lymph nodes were felt in each axilla but in no other groups. The liver was enlarged, the lower border being palpable 4 cm. below the costal margin in the right mid-clavicular line; it was smooth, firm, and slightly tender. A firm swelling could be felt descending from beneath the left costal margin; it was smooth and moved with respiration. There were no other abnormal physical signs.

*Progress.* Six days after admission to hospital an attack of haemoglobinuria took place, the early morning specimen containing large quantities of oxyhaemoglobin with a trace of methaemoglobin and much urobilinogen. No febrile reaction occurred. A similar attack followed an injection of 'Pernaemon Forte'; the injection was given in the morning, by the evening the temperature had risen to 100.8° F., and on the following morning profuse haemoglobinuria was noted. A similar train of events was observed after the intravenous injection of T.A.B. vaccine (50 millions); haemoglobinuria following the injection by nineteen hours. Immersion of the arm in ice cold water failed to provoke haemoglobinuria, nor did it follow a hot bath. Apart from these two attacks—one unexpectedly induced by 'Pernaemon Forte' and the other purposely by protein shock—haemoglobinuria always occurred without an obvious cause and without a rise in temperature or other systemic disturbance.

*Investigations.* Blood count: erythrocytes 1,940,000 per c.mm.; haemoglobin 58 per cent; colour index 1.49; reticulocytes 10.4 per cent. Marked polychromasia; moderate anisocytosis with many deeply-staining well-filled normocytes and slight poikilocytosis; platelets 135,000 per c.mm. (Kristensen's method). Coagulation time 1 min. 35 sec. at 37° C. (Dale-Laidlaw technique). Bleeding time 7 min. 30 sec. (Duke's method). Recalcified plasma clot retraction 70 per cent. of normal (Macfarlane's method). Tourniquet test faintly positive. Leucocytes 2,800 per c.mm.; neutrophil: band form 6 per cent. (168 per c.mm.); segmented 31.0 per cent. (868 per c.mm.); eosinophil 1.0 per cent.; (28 per c.mm.); lymphocyte 58.0 per cent. (1,624 per c.mm.); monocyte 4.0 per cent. (112 per c.mm.).

This count is representative and it is not necessary to reproduce subsequent counts. The haemoglobin varied between 44 per cent. and 68 per cent. and the reticulocytes between 4.2 per cent. and 16.0 per cent.

*Erythrocyte measurements.* Mean diameter: 7.27  $\mu$ ,  $\sigma$  = 0.578  $\mu$ . variability: 7.9 per cent.; microcytosis 0.2 per cent.; megalocytosis 0.0 per cent.; haematocrit 25.6 per cent.; mean corpuscular volume 116.62 cu.  $\mu$ ; mean corpuscular haemoglobin 47.29  $\gamma\gamma$ ; mean corpuscular haemoglobin concentration 40.6 per cent.; mean corpuscular thickness 2.81  $\mu$ .

*Fragility of washed erythrocytes.* 0.48–0.38 gm. sodium chloride per 100 c.c. (Whitby and Hynes' technique.) This was repeated twice and the findings were normal on each occasion.

*Sternal puncture.* The erythroblast percentage of the puncture fluid was 43.0 per cent. and the preparations were highly cellular. All erythroblasts were of the orthoplastic type, but a higher proportion than normal of

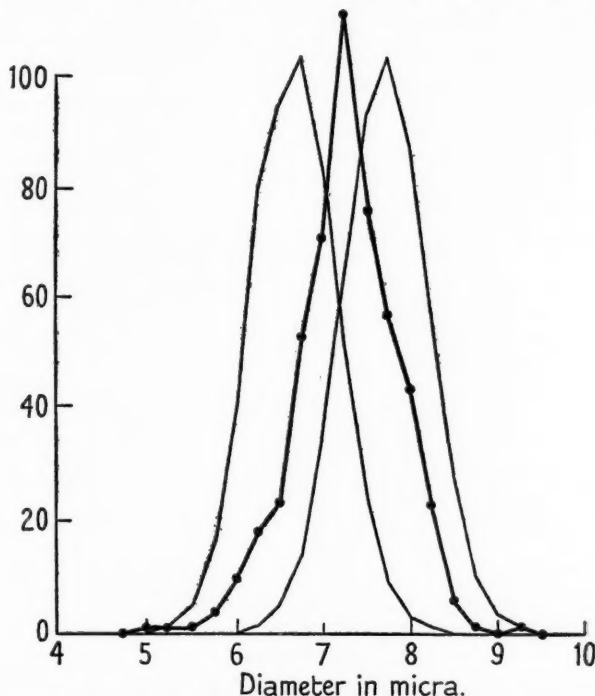


FIG. 1. Case 1 (Mrs. M. B.). Erythrocyte diameter distribution curve (Price-Jones). Mean diameter:  $7.27 \mu$ . Standard deviation:  $0.578 \mu$ . Variability: 7.9%. Microcytosis: 0.2%. Megalocytosis: 0.0%.

immature forms (pro-erythroblasts and basophilic erythroblasts) were present. No megaloblasts were seen. Granulopoiesis was normal.

*Wassermann and Sigma reactions.* Negative.

*Donath-Landsteiner reaction.* Negative. No 'cold-fixed' haemolysin could be demonstrated *in vitro* and, in addition, no haemolysis occurred when the patient's cells were incubated with her own serum in the presence of complement at  $20^{\circ}\text{C}$ .,  $37^{\circ}\text{C}$ ., and  $42^{\circ}\text{C}$ .

*Van den Bergh's reaction.* Haemolysis occurred directly the blood was drawn on three occasions, but the indirect reaction by van den Bergh's original technique gave a reading of only 0.7 units. On a fourth occasion when no haemolysis occurred the direct reaction was negative and the indirect less than 0.4 units. There had been no haemoglobinuria preceding this test.

*Urine.* In the intervals between the bouts of haemoglobinuria the specific gravity varied between 1010 and 1024; the diurnal output was normal; no coagulable protein nor reducing substance was present. Urobilinogen was occasionally found but bilirubin never. Even when haemoglobinuria was

absent considerable quantities of free iron could always be demonstrated. Spectroscopy of the urine during the attacks constantly showed oxyhaemoglobin with a trace of methaemoglobin; myohaemoglobin was never found. Occasional leucocytes and granular casts were present in the centrifugized deposit between the bouts of haemoglobinuria. Erythrocytes were not present at any time.

*Laevulose tolerance test.* Within normal limits.

*Gastric analysis.* Low secretion of HCl to histamine.

*Oral cholecystography.* No filling of gall-bladder.

*Cystoscopy and excretion pyelography.* Normal.

*Further progress.* Occasional attacks of haemoglobinuria which were almost always nocturnal continued but the patient's condition remained stationary; these attacks were always followed by mild jaundice lasting 1-2 days. On 28 July 1936 a blood-transfusion of 100 c.c. of citrated blood was given in order to determine whether this form of therapy was likely to produce haemoglobinuria; the urine remained clear afterwards and no pyrexia or other ill effect was noted. Accordingly, the decision was made to transfuse repeatedly, and on 7 August 1936 a second transfusion of citrated blood was undertaken, after 350 c.c. had been administered the patient complained of severe pain in the chest and epigastrium, the transfusion was stopped immediately, but the temperature rose to 101.5° F. and she had a slight rigor. Within twenty-four hours a heavy haemoglobinuria had appeared and the urine remained discoloured for a further twenty-four hours. In view of the dangers attendant upon transfusion splenectomy was advised, and this was performed by Mr. J. B. Hume on 12 August 1936. At operation it was found that the swelling palpable in the left hypochondrium was an abnormally shaped left lobe of the liver and that the spleen was not appreciably enlarged. Following splenectomy she developed a sterile pleural effusion on the left side and an infection of the urinary tract due to *B. proteus*. The latter persisted and did not yield to mandelic acid nor to Prontosil, but her clinical condition showed little change and she had no haemoglobinuria and no increase in her anaemia.

On 1 October 1936 she suddenly complained of headache and became dysphasic, but these symptoms lasted only three-quarters of an hour; no signs of organic disease of the central nervous system were apparent at the time or subsequently. On 5 October 1936 she began to experience pain and tenderness in the right loin; the temperature rose abruptly to 103° F. On the following days the urine contained gross blood in addition to a heavy deposit of pus. The blood urea rose to 80 mg. per 100 c.c. on 9 October 1936, and three days later she died in coma.

*Pathology.* Operation specimen. A spleen measuring 11 x 5 x 3.5 cm. and weighing 155 gm. The external surface was smooth; the splenic vessels showed no abnormality and there were no lymph nodes at the hilum. The cut surface showed a dark red pulp in which the widely separated Malpighian bodies were easily seen. The trabeculae and vessels were natural and there was no infarction. The histological appearances are described in a later paragraph.

*Summary of post-mortem examination.* The body of a well-nourished woman; no jaundice; healed left paramedian and inguinal abdominal operation scars.

*Brain.* There was a thrombosis of the left temporoparietal vein with petechial haemorrhages in the adjacent brain substance but no macroscopic areas of softening.

*Heart.* Nothing remarkable.

**Lungs.** The left pleural cavity showed some old adhesions and contained a small clear effusion; both lungs were slightly oedematous.

**Peritoneum.** There were a few old adhesions over the liver and in the splenic region. No portal vein thrombosis.

**Liver.** 1,890 gm. There were irregular areas of fatty change; the organ as a whole was of a red-brown colour but gave a negative Prussian Blue reaction. Many of the smaller branches of the hepatic veins were thrombosed, but the inferior vena cava was natural. The gall-bladder was distended with pale bile.

**Stomach and intestinal tract.** Natural.

**Spleen.** Removed. No splenunculi.

**Kidneys.** These were greatly enlarged and congested. The capsule stripped easily leaving a surface covered with multiple small abscesses of a green colour. The cut surface showed a severe degree of suppurative pyelonephritis and the intervening kidney tissue was snuff-coloured. The Prussian Blue reaction was strongly positive in the cortex and interpyramidal substance but negative in the pyramids. There was severe pyelitis, ureteritis, and cystitis with sloughing of the mucous membrane. The urine was turbid but not obviously blood-stained.

**Bone-marrow.** The femoral marrow was a faint pink in the upper two-thirds of the shaft and the vertebral and sternal marrow bright red.

Examination of the colonic faeces *post mortem* showed no excess of stercobilin.

**Microscopic examination.** Only those organs showing pathological lesions are described. In addition to the usual histological stains the following methods were used in the identification of pigments.

**Prussian Blue reaction.** Gömöri's (1936) method was used. The iron pigment, which is probably ferric oxide, is found either in a diffuse form—the cytoplasm of the cell staining a uniform blue—or in the form of granules of varying sizes.

**Benzidine reaction.** Lephehne's (1920) method was applied to frozen and paraffin sections of formol-fixed material. Erythrocytes take a dark brown colour and a similar colour is given by the brown pigment which is found in the renal tubules following the haemoglobinuria resulting from incompatible blood transfusion. This is regarded by Baker (1937) as haematin. Iron pigment gives no reaction.

**Lipoid stains.** Sudan III and Nile Blue sulphate were used.

Haematoidin is identified by exclusion; the characteristic yellow-brown crystals failing to react with fat stains or to the Prussian Blue reaction. Gmelin's reaction was not employed.

**Lipofuscin.** Pigment granules lying around the nuclei of the liver cells which give no iron reaction but stain feebly with Sudan III and Nile Blue sulphate and can be bleached with hydrogen peroxide are considered to be of this nature.

**Bile pigment.** This is identified in part by the topographical arrangement of the pigment masses and in part by its colour in unstained sections.

**Spleen.** The normal architecture is maintained. The Malpighian bodies are large and many show Flemming's centres; there is considerable hyaline degeneration of the follicular arterioles but no fibrosis of the follicles themselves. In the pulp the reticulum-cell framework is compressed by a generalized dilatation of the venous sinuses. These contain erythrocytes and leucocytes; the littoral cells are enlarged but show no budding off or erythrophagocytosis. The thickness of the reticulin framework is slightly increased but there is no increase in collagen.

Iron pigment is present in the diffuse form in some of the littoral cells, and in the follicles and around the branches of the splenic artery there are a few histiocytes containing granular iron pigment, but the degree of siderosis is slight.

**Brain.** Partially occluding a meningeal vein is a fibrin thrombus in which there is enmeshed a number of erythrocytes and leucocytes. In addition there are large numbers of round bodies, measuring between 2 and 8  $\mu$  in diameter which stain feebly with basic or acid dyes and have a granular appearance. They fail to give either the Prussian Blue or Lepehne's reaction. There are also a few histiocytes containing iron pigment in the diffuse form, and around the edge of the thrombus there are histiocytes containing a bright yellow pigment, probably haematoidin. The vein wall presents no abnormality. The smaller vessels in the brain substance contain similar thrombi, but the distribution is focal and no abnormality in wall or content is observed in arteries or capillaries.

The brain substance shows the changes associated with a recent vascular occlusion—diffuse oedema, areas of haemorrhage, and softening.

**Lungs.** Generalized oedema and focal anthracosis. Some of the smaller vessels are occluded by fibrin thrombi similar to those described in the brain, and megakaryocytes are lodged in some of the alveolar capillaries. The alveolar phagocytes give a diffuse iron reaction.

**Intestinal tract.** Neither the stomach, small intestine, or colon show any abnormality or iron pigment.

**Liver.** Throughout the liver there is a central zonal necrosis; it varies in intensity and in the most severe lesions there is almost always a thrombosis of the branch of the hepatic vein. The slightest lesion is merely a congestion of the capillaries and marks deposition of pigment (resembling lipofuscin) in the central portion of the lobule; in the more advanced lesions there is irregularity of cell outline with the appearance of fatty droplets in the cytoplasm, nuclear pyknosis, and, finally, loss of the nucleus and cell outline. The extent of the necrosis around the central veins varies, but there are always a few normal cells at the periphery of the lobule. With Nile Blue sulphate the fatty droplets stain a dark blue in the central portion and at the periphery of the necrosis a red-violet. The sinusoids in the necrotic area are dilated and congested with erythrocytes and neutrophils. In places the erythrocytes are so closely packed as to appear agglutinated, they are associated with clusters of thrombocytes and a fibrin network. The thrombi in the central veins are almost pure fibrin thrombi. With Lepehne's stain only a proportion of the clumped erythrocytes stain dark brown; other cells resembling erythrocytes stain feebly or not at all. The Kupffer cells are swollen throughout the sinusoids and a few contain round eosinophilic inclusions which do not give Lepehne's reaction. All the Kupffer cells give a diffuse iron reaction, and in a few there are iron pigment granules. None of the liver cells show any iron pigment, and the only pigment seen in them is the yellowish-brown material in the central portion of the lobule which is regarded as lipofuscin. There is no biliary retention.

**Kidney.** The renal lesion is complicated and somewhat obscured by a severe pyelonephritis with abscess formation. The glomeruli present no abnormality. The convoluted tubules show a severe albuminous degeneration of the epithelium with a granular cytoplasm and eosinophilic exudate in the lumina. In the distal portions of the convoluted tubules and the ascending loops of Henle the degenerative change is less, but pigment granules are present in the epithelium and in the lumina. This pigment

is irregular in amount and in distribution. The collecting tubules show no abnormality and no pigment within the cells or the lumina. Apart from the pyelonephritis the interstitial tissues show no abnormality. A few of the vessels contain hyaline thrombi, but these are usually in relationship with inflammatory areas. No fibrin thrombi are seen in the capillaries. Gömöri's reaction shows no iron pigment in the glomeruli, a diffuse reaction in the proximal convoluted tubules and coarse granular haemosiderin in the distal convoluted tubules and the loops of Henle. No iron pigment is present in the rest of the tubular tract and Lepehne's reaction is negative throughout.

Lymph node. There is a moderate proliferation of the littoral cells but no abnormality of the follicles or medulla. A few of the littoral cells contain granular iron pigment.

Bone-marrow. The marrow as a whole is of low cellularity with a predominance of adipose tissue, but there are highly cellular areas in which the adipose tissue has been obliterated and the capillaries and sinusoids obscured. Erythropoietic marrow is in excess of leucopoietic and there is an increase of immature forms (basophilic and polychromatic erythroblasts) but erythropoiesis appears to be orthoplastic. Mitoses in the erythroblasts are not numerous. Megakaryocytes are scanty. A few of the histiocytes show erythrophagocytosis and some give a diffuse iron reaction but there is no granular iron pigment.

*Case 2.* Mrs. D. B., aged 36 years. A housewife, admitted to St. Bartholomew's Hospital in August, 1936. The patient had always been healthy and robust; she remembered no previous illnesses and had never been engaged in employment other than her housework. She came from a healthy family of nine children. There was no family history of jaundice or anaemia. Three years before coming under observation she had noticed that her eyes had become yellow and that subsequently the yellowness had spread over her body. The stools had remained normal in colour, but she had noticed that her urine was darker than normal. During the succeeding 2½ years this change had gradually increased, but at no time had she felt ill.

Six months before she had sought medical advice on account of her persistent yellow colour. She was found to be severely anaemic and was given a blood transfusion. Following this she had some epistaxis but otherwise showed no change. Daily injections of liver extract were given without improvement and later another blood transfusion. She remained well for four days after this and then developed vague muscular pains across the shoulders; a week later her urine became bright red in colour and remained the same until she came under our observation three months before her death. When seen at that time the patient was grossly pigmented a dark brown and the sclerotics showed the same colour. There was marked pallor of the mucous membranes. She felt very weak, but otherwise had no complaints. The tongue was normal and there were no enlarged lymph nodes in the neck although a few small ones were palpable in each axilla. The lungs and cardiovascular system showed no abnormality. The spleen was easily palpable about two fingers' breadths below the costal margin; it was firm in consistency. The liver was enlarged down to the level of the umbilicus; its consistency was firm. There were no enlarged nodes in the groins, and the legs showed no abnormalities. The urine was dark brown in colour and contained free oxyhaemoglobin, methaemoglobin, and a great excess of urobilinogen. In the deposit were large numbers of small pigmented casts but no cells. A blood count showed a marked anaemia; on admission the erythrocytes were

1,770,000 per c.mm. and the haemoglobin 28 per cent.; the reticulocytes varied between 25 per cent. and 40 per cent. After two weeks the haemoglobin fell to 18 per cent. and a transfusion of 600 c.c. of citrated blood was given. No ill effects were observed but the haemoglobin never rose above 28 per cent. and then began to fall again. A continuous drip transfusion of

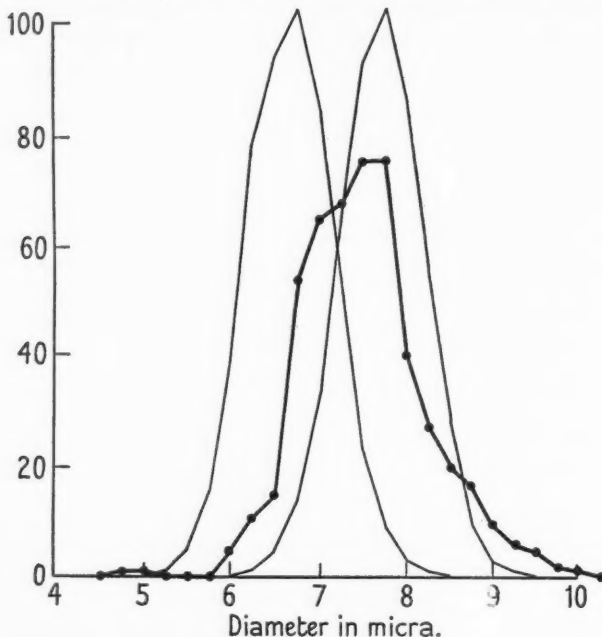


FIG. 2. Case 2 (Mrs. D. B.). Erythrocyte diameter distribution curve (Price-Jones). Mean diameter:  $7.70\mu$ . Standard deviation:  $0.632\mu$ . Variability: 8.2%. Microcytosis: 0.4%. Megalocytosis: 5.6%.

3,600 c.c. of citrated blood was then given which raised her erythrocytes to 4,050,000 per c.mm. and her haemoglobin to 85 per cent. She was much improved by this and two weeks later the haemoglobin was still as high as 71 per cent. and no increase in the output of haemoglobin in the urine had been noted, although daily variations occurred throughout the course of the disease. At this time she had thirteen teeth extracted on account of marked pyorrhoea alveolaris. Subsequently the pigmentation diminished and the urine became less dark. She was allowed to return home and remained well for three weeks when she developed a whitlow on the left thumb. Following this there was a marked increase in the pigmentation and in the darkness of the urine and she returned to hospital. There was no change in the physical signs but she had developed slight oedema of both ankles. The thumb was treated surgically and thick pus evacuated. The erythrocytes were 2,550,000 per c.mm. and the haemoglobin 53 per cent. The urine now showed a curious change: during the day it was normal in colour but each night specimen contained a large amount of oxyhaemoglobin. This nocturnal haemoglobinuria continued for several weeks but finally the haemoglobinuria again became continuous. The patient became progressively more anaemic; she developed venous thrombosis in both legs and later in the right arm which

caused extreme pain and discomfort. Pyrexia appeared, she became progressively weaker and died with pericarditis and pulmonary oedema on 17 November 1936.

*Investigations.* Blood count: erythrocytes 1,200,000 per c.mm. haemoglobin 23 per cent.; colour index 0.96; reticulocytes 30 per cent.; marked polychromasia, but erythrocytes otherwise normal; leucocytes 4,000 per c.mm.; neutrophil 61.0 per cent. (2,440 per c.mm.); eosinophil 3.0 per cent. (120 per c.mm.); basophil 1.0 per cent. (40 per c.mm.); lymphocyte 35.0 per cent. (1,400 per c.mm.).

*Erythrocyte measurements.* Mean diameter:  $7.70 \mu$ .  $\sigma = 0.632 \mu$ . variability 8.2 per cent.; microcytosis 0.4 per cent.; megalocytosis 5.6 per cent.

*Fragility of washed erythrocytes.* 0.45 to 0.30 gm. Sodium chloride per 100 c.c. (Whitby and Hynes' technique.)

*Plasma.* The blood plasma contained free oxyhaemoglobin, methaemoglobin, and urobilinogen. There were no abnormal pigments in the blood cells.

*Donath-Landsteiner reaction.* Negative.

*Van den Bergh's reaction.* Direct: negative. Indirect: 10 units.

*Wassermann and Sigma reactions.* Negative.

*Gastric analysis.* Achlorhydria to histamine.

*Urine.* The pigments in the urine were shown to be oxyhaemoglobin, methaemoglobin, and an excess of urobilinogen. No myohaemoglobin was observed at any time. There was always a large quantity of free iron present in the urine which was independent of the amount of haemoglobin present.

*Pathology.* Summary of post-mortem examination. The body of a well-nourished woman showing a slight degree of jaundice. Healing whitlow of left thumb-nail bed.

*Brain.* Natural.

*Heart.* Fibrinous pericarditis with bile-stained effusion. Considerable dilatation of the right chambers. No valvular abnormalities.

*Lungs.* Bile-stained pleural effusion on left. Oedema of both lungs.

*Peritoneal cavity.* Contained about 1,000 c.c. of bile-stained fluid.

*Alimentary tract.* Natural.

*Liver.* 2,525 gm. The surface was natural; the cut surface was fatty and showed small radiating light yellow areas around the branches of the hepatic veins. This appearance was present throughout the liver but varied in intensity in its various portions. There was no evidence of hepatic vein thrombosis and no macroscopic free iron.

*Spleen.* 265 gm. No perisplenitis. Follicles and medullary tissues clearly differentiated. A moderate degree of congestion. No infarction. Normal consistency. No free iron macroscopically.

*Kidneys.* Left: 320 gm. Right: 300 gm. Considerably enlarged; the capsule stripped easily leaving a brownish surface in which the stellate veins were prominent. The cut surface was snuff-coloured in the cortex and the interpyramidal medullary portion, but the pyramids were a normal dark red. The cortex was slightly broadened, showed no fibrosis and the cortico-medullary demarcation was sharp. There was no evidence of infarction, past or present. The pelvis and blood vessels appeared natural. The macroscopic reaction for free iron was strongly positive in the cortex and interpyramidal medullary portion but negative in the pyramids. The ureters and bladder were natural and the urine was clear.

*Bone-marrow.* Red marrow occupied the whole length of the femoral shaft; the marrow of the ribs, sternum, and vertebral bodies was dark red.

The veins of the arms were examined but no thrombosis could be found.

*Microscopic examination.* The histological appearances will be described briefly as they are almost identical with those of Case 1; only the differences will be emphasized.

**Lungs.** There is an acute oedema. Megakaryocytic emboli are present in the alveolar capillaries in moderate numbers, but there are no thrombi. Very few alveolar phagocytes are seen, but they all give a diffuse reaction for free iron.

**Breast.** There is no iron pigment in the ducts.

**Liver.** There is a generalized central zonal necrosis which is more evenly distributed than in Case 1, but nowhere so severe. There are no thrombi or erythrocytic agglutinations although the dilated capillaries are congested and contain in addition to leucocytes and erythrocytes round bodies about  $8\mu$  in diameter. These bodies show faintly eosinophilic granules but give neither Gömöri's nor Lepehne's reaction. In these sinusoids fibrin coagula are present. The central degenerate liver cells contain much fat and also a brownish pigment which is probably lipofuscin. The normal liver cells at the periphery of the lobules contain iron pigment in the granular form, and in this region the Kupffer cells give a diffuse reaction but do not show any erythrophagocytosis. Elsewhere the Kupffer cells are natural. There is a little bile retention in the biliary capillaries.

**Spleen.** The Malpighian bodies are small and the central arterioles show hyaline degeneration. There is a moderate amount of medullary congestion and the venous sinuses are somewhat compressed. There is no erythrophagocytosis. The perivascular histiocytes contain a little granular iron pigment. There is no fibrosis.

**Kidney.** The appearances are identical with those in Case 1 save that there is no pyelonephritis. The glomeruli are natural. The convoluted tubules show a severe albuminous degeneration, and in their more distal portions and the ascending loops of Henle contain granular pigment both in the lining cells and free in the lumina. The collecting tubules are natural. The haemosiderin is in the diffuse form in the proximal and in the granular form in the distal tubules, but in the collecting tubules there is none. Lepehne's reaction is negative throughout.

**Bone-marrow.** The marrow is extremely cellular and very little adipose tissue is present. There is a marked excess of erythropoietic over leucopoietic elements. Basophilic and polychromatic erythroblasts are increased, but erythropoiesis is orthoplastic throughout. Mitotic figures are not numerous in the erythroblasts. Islets of lymphoid tissue are not seen but megakaryocytes appear in normal numbers.

#### *Clinical and Haematological Aspects.*

The excellent reviews of Witts (1936) and Hamburger and Bernstein (1936) have rendered a detailed discussion of the clinical features of the syndrome superfluous. The two instances reported here have shown the typical features of the disease; firstly, haemoglobinuria which may be constant over long periods or may be paroxysmal but, if the latter, almost always nocturnal; secondly, an anaemia which is presumably determined by haemolysis; thirdly, the persistent presence of free iron in the urine even when haemoglobin is lacking; and, fourthly, a predisposition to venous thromboses. The prolonged course of the complaint and the obstinate lack of response to treatment are

equally characteristic. Splenectomy was performed in one patient but, although no haemoglobinuria occurred afterwards, she died from pyelonephritis. The blood picture merits a more detailed consideration. In both cases there was anaemia with leucopenia; the latter being due mainly to a reduction of neutrophils. No abnormal leucocytes were seen. In Case 1 the anaemia was hyperchromic but, although the mean corpuscular volume was raised, the mean diameter of the erythrocytes was within the limits of normality. The mean corpuscular thickness estimated from these data was  $2.809 \mu$  (Normal  $1.729-2.545 \mu$ , Price-Jones, Vaughan, and Goddard 1935). In Case 2 the anaemia was orthochromic and the mean diameter of the erythrocytes within normal limits although the variability was increased, a finding probably related to the more severe anaemia shown by this patient. Both cases showed a persistent reticulocytosis and in both erythrocyte fragility to saline was normal. In Case 1 thrombocytopenia and a positive tourniquet test were noted. These haematological findings are in accord with those of other published cases; they are clearly compatible with a diagnosis of haemolytic anaemia, and sternal puncture performed in one case showed an erythroblastic hyperplasia with the 'shift to the left' of erythropoiesis so frequently seen in chronic haemolytic anaemia.

The mechanism of haemolysis in the Marchiafava-Micheli syndrome remains unexplained. The bouts of haemoglobinuria are unrelated to exertion and, though an individual attack may be occasioned by an acute infection, there is nothing to suggest that the disease is a manifestation of an infective or toxic process. The negative Donath-Landsteiner reaction distinguishes the condition from paroxysmal haemoglobinuria *e frigore* with its 'cold-fixed' autohaemolysin and the pigment in the urine is always haemoglobin and not myohaemoglobin. Thus all other recognized causes of haemoglobinuria may be discounted. It is of interest that in Case 1 on three occasions marked haemolysis was found in blood withdrawn from a vein although there was no haemoglobinuria at the time. It is possible that haemolysis had taken place *in vitro* although subsequent efforts to produce this phenomenon were unsuccessful. A similar finding has been recorded by Salén (1927).

There is a tendency on the part of some haematologists to dismiss many unusual cases of haemolytic anaemia as atypical examples of familial haemolytic icterus. For this reason, perhaps, we may be excused for labouring the marked differences between the two conditions. There can be no reasonable doubt that the Marchiafava-Micheli syndrome is a disease *sui generis*: the absence of a family history, the normocytosis, haemoglobinuria, and haemoglobinaemia, the persistent haemosiderinuria, the normal erythrocyte resistance to saline, and the failure of splenectomy to influence the course of the disease process are in strong contrast to the familial incidence, spherocytosis, excessive erythrocyte fragility, and beneficial results of splenectomy in acholuric jaundice. Examination of the plasma during the attacks of haemoglobinuria has constantly shown the presence of considerable quantities of oxyhaemoglobin with traces of methaemoglobin; abnormal pigments have

not been found in the erythrocytes. In many cases these pigments are present in the plasma in the absence of haemoglobinuria. One of us (E. F. S.) has examined the plasma from three cases of familial acholuric jaundice and has found only the trace of oxyhaemoglobin which can be demonstrated in every specimen of plasma that is subjected to spectroscopy; methaemoglobin was not present. This extra-cellular methaemoglobinaemia is another probable point of distinction between these two types of haemolytic anaemia. In Case 1 the discrepancy between the degree of anaemia and the apparent mildness of the haemolytic process was a salient clinical feature, and it seems probable that this must be explained by a continued haemolysis of degree insufficient to produce haemoglobinuria. At times an accentuation of this process would lead to a paroxysm in which haemoglobin was excreted in the urine. This concept suggests the possible existence of mild grades of the Marchiafava-Micheli syndrome in which haemolysis is never sufficiently intense to produce haemoglobinuria. It would be unwise to pursue this conjecture too far, but we would suggest that when cases of chronic acquired haemolytic anaemia are encountered the plasma be examined for methaemoglobin and the urine for free iron.

#### *Pathological Aspects*

Although eleven of the twenty-eight recorded examples of this syndrome were dead at the time of the report, pathological accounts are given only in seven and several of these lack detail. Of the nine cases in which splenectomy had been performed the appearances of the spleen are available only in six. (It has not been possible to read the original accounts of two of these cases, Saxl (1930) and Donati (1930), which are mentioned by Hamburger and Bernstein, (1936)). The pathological findings in the published cases and in those reported here have been arranged in tabular form and the close similarity between the cases is at once apparent. The main features may be summarized as follows:

1. Venous thromboses both in the systemic and portal circulation.
2. Hepatomegaly (average weight 2,010 gm.) with central zonal necrosis.
3. Moderate splenomegaly (average weight 344 gm.) with little histological deviation from the normal.
4. Enlarged kidneys of a snuff-brown colour and showing considerable cloudy swelling.
5. A bone-marrow showing marked erythropoietic hyperplasia of an orthoplastic type.
6. Haemosiderosis of unusual distribution; free iron pigment being present in the convoluted tubules and ascending loops of Henle in the kidneys in large amounts but in other organs only in traces.

These changes represent merely the changes following prolonged intravascular disintegration of erythrocytes and they throw no light on the aetiology of the syndrome. The lesions which have been detailed as characteristic of the Marchiafava-Micheli syndrome contrast sharply with those of

acholuric jaundice where the splenomegaly is of a higher order—average weight 900 gm.—and where there is marked siderosis of the liver and spleen as well as of the kidneys. The pathological lesions found in the Marchiafava-Micheli syndrome can be divided into those resulting from the presence of erythrocyte stromata in the circulation and those due to the haemoglobinaemia.

*Lesions produced by erythrocyte stromata.* Pearce (1904) was one of the first to show that the injection into an animal of serum rich in haemagglutinins induced a hepatic necrosis and he suggested that the lesions were due to the impaction of agglutinated erythrocytes in the liver sinusoids with the formation of hyaline thrombi. These experiments have been repeated by different investigators, but until recently there was a lack of agreement with Pearce's explanation. It was suggested that the hepatic necroses might be due to the free haemoglobin or to the haemolysin exerting a direct toxic action on the liver cells, or that they might result from intravascular clotting. Similar liver lesions are seen in Blackwater Fever (Stephens, 1937) and following transfusions of incompatible blood (Goldring and Graef, 1936). Some investigations of Hjärre (1930) into the nature of the puerperal haemoglobinuria of cows are of interest in this connexion. This disease occurs in cows a few weeks after calving and is characterized by an acute anaemia with haemoglobinuria and a high mortality. Its aetiology is obscure but the disease is in some way related to the intensity of milk production. *Post mortem* there is a focal necrosis of the liver and extreme siderosis of the liver, spleen, and kidneys. Hjärre, in an attempt to reproduce the lesions experimentally, showed that central focal necrosis could be produced in animals by the injection of haemolysins or of lysed blood yet no liver damage followed the injection of isotonic solutions of haemoglobin. Further, typical focal necroses were produced by the injection of erythrocyte stromata or inert particles such as lycopodium powder into the mesenteric veins. If erythrocyte stromata were injected into the systemic circulation, emboli were found in the alveolar capillaries but no hepatic changes were observed. These experimental lesions so closely resemble those seen in the liver in the Marchiafava-Micheli syndrome that it is reasonable to suppose that the hepatic necrosis in this disease is in large part a mechanical effect produced by blockage of the liver sinusoids by agglutinated erythrocytes and erythrocyte stromata. In these sinusoids, in addition to erythrocytes and leucocytes, round bodies are seen which resemble the erythrocyte stromata found after haemolysis *in vitro*. The frequency with which the hepatic veins alone show thrombosis suggests that the portal system is the common site of haemolysis, but that local systemic venous thrombosis may also occur is shown by the cerebral lesion in Case 1 as well as by many recorded cases. The round bodies which we have regarded as erythrocyte stromata were also seen in the cerebral capillaries in the vicinity of the venous thrombosis in Case 1; this observation suggests that haemolysis may take place throughout the vascular system, but that agglutination and thrombosis require some local

## Summary of Pathological Data in Case of the Ma

Authors.	Patient's Age.	Sex.	Cause of death.	Thromboses.	Lungs.	
Marchiafava and Nazari (1911). Case 3	31	M	Influenzal bronchitis	None	Bilateral pleural effusions	525 gm. colour. centre, y phery. A erosis, fa and a y possibly iron. 0- weight 350 gm. Hist. nat
Biffis (1915). Case 5. Sisto (1915). Case 3	28	M	Splenectomy followed by death in a few hours	None	Natural	
Panton et alia (1924). Case I	38	M	Sore throat and septicaemia	During life		Characteristic changes o
Salén (1927)	52	M	Broncho-pneumonia	None	Broncho-pneumonia	2,100 gm in centr negative stain it blue-vio
Enneking (1928)	37	M	A few hours after operation for mesenteric thrombosis	Mesenteric veins. Infarcts of intestine	—	2,050 gm Hist. ce fatty c cells c erythro globin Medium merous no free retenti
Barta and Görög (1929)	34	M	Pulmonary embolus three weeks after splenectomy	Pancreatic, splenic, and portal veins. Infarct of small intestine. Peritoneal effusion	Pulmonary embolus	
Marchiafava (1931)	23	M	Anaemia and asthenia, a year after splenectomy	—	—	Normal change with b in Ku iron
Bergmark (1931)	40	M	Died 12 hours after cholecystectomy for cholelithiasis	Portal vein, sigmoid and longitudinal venous sinuses	Hyaline thrombi in capillaries. Haemorrhagic pericarditis	Hist. t vein. old an
Rosenthal (1932)	52	M	Following splenectomy. No P.M.	—	—	

\* Case of Salén. Miller's stain is a modification of Benda's myelin stain and was regarded by Miller as specific

## Case of the Marchiafava-Micheli Syndrome

Liver.	Spleen.	Kidney.	Marrow. Lymph nodes.
325 gm. Pale yellow colour. Lobules red at centre, yellow at periphery. <i>Hist.</i> central necrosis, fatty infiltration, and a yellow pigment, possibly biliary. No free iron. 0.00617 % Fe wet weight	270 gm. 18 × 8.5 cm. Dark red. Homogeneous. <i>Hist.</i> cent. fibrinoid necrosis of Malpighian bodies. Medulla natural. No free iron. 0.00926 % Fe wet weight	L. 430; R. 425 gm. Cortex dark brick red. Medulla greyish. Fatty tissue natural. <i>Hist.</i> siderosis of convoluted tubules and loops of Henle, pigment in cells and lumen. 0.0864 % Fe wet weight	Intense red marrow. <i>Hist.</i> active normoblastic erythropoiesis. Megakaryocytes scarce. No free iron. Slight siderosis of sinus-lining cells in lymph nodes
350 gm. Pale red brown, <i>Hist.</i> natural	280 gm. <i>Hist.</i> Malpighian bodies natural. Venous sinuses congested. No free iron	Normal size. Pale red with a dark red-brown cortex. <i>Hist.</i> siderosis of tubules. Increase of interstitial tissue	Red cellular marrow in rib, humerus and femur. <i>Hist.</i> normoblastic hyperplasia. Megakaryocytes scarce. Hyperplasia of lymph nodes with proliferation of histiocytes. No free iron
<i>Changes of pernicious anaemia in addition to those of sepsis.</i>			
2100 gm. <i>Hist.</i> pigment in centre of lobule. Iron negative. With Miller's * stain it varies from green-blue-violet	Infective type of spleen. No free iron	Normal weight. <i>Hist.</i> siderosis of convoluted tubules and loops of Henle. Iron containing casts in collecting tubules. A little arterio-sclerotic change	—
2050 gm. A little fatty. <i>Hist.</i> central necrosis with fatty change. Kupffer cells contain occasional erythrocyte or haemoglobin droplet	Macroscopic natural. <i>Hist.</i> no erythrophagocytosis	400 gm. natural naked-eye. <i>Hist.</i> degeneration and siderosis in convoluted tubules. A few hyaline casts	Bone-marrow red
Medium size, brown. Numerous thromboses. <i>Hist.</i> no free iron. A little bile retention	720 gm. 18 × 11 × 5 cm. Capsule thickened, soft, dark red, full of blood. <i>Hist.</i> follicles natural. Sinuses empty. Patchy congestion of pulp. No free iron	Thrombosis of small renal veins. Much free iron	Humerus fatty. <i>Hist.</i> low cellularity, very few nucleated erythrocytes. No megakaryocytes. No free iron. Ribs more cellular
Normal size. <i>Hist.</i> fatty change in centre of lobule with biliary pigment. Fat in Kupffer cells. No free iron	130 gm. Natural naked-eye. <i>Hist.</i> hyaline degeneration of follicular arterioles and sclerosis of follicles. Desquamation of sinus lining cells. No free iron	230, 270 gm. Extreme siderosis of convoluted tubules and loops of Henle	Marrow. Moderately active normoblastic erythropoiesis. No free iron. Lymph nodes. No free iron
<i>Hist.</i> thrombi in portal vein. Miliary necroses, old and recent	520 gm. <i>Hist.</i> cellular medulla with increase in connective tissue, very little pigment. Enlarged. <i>Hist.</i> small follicles. Pulp not congested. Sinuses dilated with thickening of walls. Contain free littoral cells. No free iron	Scars from old infarcts, siderosis of convoluted tubules	Marrow is red
—	—	—	—

specific for methaemoglobin, but has been shown by Hueck not to be specific but merely a lipid stain.

## Summary of Pathological Data in Case of the Ma

Authors.	Patient's Age. Sex.	Cause of death.	Thromboses.	Lung.	
Schalty (1935)	25 F	Alive four years after splenectomy	—	—	
Witts (1936)	29 F	Death seven hours after splenectomy due to haemorrhage from the pedicle	—	—	Hist. slight ing, cen gestion. adjoining lobular trophy o
Hamburger and Bern- stein (1936). Case 2	28 M	Alive three months after splenectomy	—	—	
Bodley Scott, Robb- Smith and Scowen (1937). Case 1	52 F	Pyelonephritis, two months after splenec- tomy	Meningeal vein	Oedematous. L-side effusion. Hist. hya line thrombi in capi laries. Megakaryo cytic emboli. Diffus iron reaction in al veolar phagocytes	1,890 gm areas. branches Hist. cer congesti and thr hepatic ment of occasio cytosis. iron in Lipofus cells
Bodley Scott, Robb- Smith and Scowen (1937). Case 2	36 F	Anaemia, asthenia	Observed in life	Oedematous. L-side effusion. Hist. no thrombi. Mega- karyocytic emboli	2,525 gm areas. crosis engorge occasio fuse iron and gra pheral fuscin cells, sl

## Case of the Marchiafava-Micheli Syndrome (continued)

Liver.	Spleen.	Kidney.	Marrow. Lymph nodes
—	'Size of two fists.' <i>Hist.</i> large follicles with secondary centres. Congestion of pulp with wide sinuses	—	—
<i>Hist.</i> slight cloudy swelling, central zonal congestion. Pigment in cells adjoining dilated intralobular veins, hypertrophy of Kupffer cells	<i>Hist.</i> reticular hyperplasia, partial closure of sinuses, anaemia of pulp. Pressure atrophy of follicles. Hypertrophy of sinus cells. No increase of iron pigment. Increase of primitive granular cells and nucleated erythrocytes	—	<i>Hist.</i> cellular marrow with increased erythropoietic activity. High plasma cell content. No increase of iron pigment
—	306 gm. Sinuses contained a moderate amount of blood. Pulp natural	—	—
side hyp api ryo fus a os 2,890 gm. Irregular fatty areas. Thromboses of branches of hepatic vein. <i>Hist.</i> central necrosis with congestion of sinusoids and thrombi of fibrin in hepatic veins. Enlargement of Kupffer cells with occasional erythrophagocytosis. A little diffuse iron in Kupffer cells. Lipofuscin in central liver cells	155 gm. Naked-eye natural. <i>Hist.</i> slight degree of diffuse reticulin increase. Sinusoids empty. Malpighian bodies natural. No free iron	Enlarged. Dark red-brown cortex. Severe pyelonephritis with abscess formation. <i>Hist.</i> siderosis of convoluted tubules and loops of Henle. No haematin	Femur. Faint pink upper two-thirds of cavity. Vertebrae and sternum red. <i>Hist.</i> Active orthoplastic erythropoiesis
side no ga i 2,525 gm. Focal yellow areas. <i>Hist.</i> central necrosis with sinusoidal engorgement but only occasional thrombus. Diffuse iron in Kupffer cells and granular iron in peripheral liver cells. Lipofuscin in central liver cells, slight bile retention	265 gm. Naked-eye natural. <i>Hist.</i> moderate congestion of medulla. Follicles natural. Trace of free iron in medulla	320; 300 gm. Red-brown cortex. Pyramids normal. <i>Hist.</i> siderosis of convoluted tubules and loops of Henle. No haematin	Red marrow whole length of shaft of femur, sternum, ribs, and vertebrae. <i>Hist.</i> very active orthoplastic erythropoiesis

factor such as slowing of the circulation for their production. If partial stagnation be a factor in the production of haemolysis its occurrence at night may be related to the slowed circulation rate of sleep.

*Distribution of haemoglobin and its derivatives in the organs.* One of the many anomalies of this syndrome is the distribution of the iron pigment in the organs. The kidneys show an extreme siderosis but other tissues only show histological traces. It is clear that the iron metabolism and the iron content of the organs in this disease require further study; the only available figures are those of Marchiafava (1911) which have little value as they are expressed in percentages of the fresh weight of the organs.

In other conditions, spontaneous or experimental, associated with haemolysis the iron content of the liver, spleen, and kidneys is roughly proportional. In the later stages of recovery from an acute haemolytic anaemia there is retention of iron pigment in the kidney long after it has been absorbed from the other organs in the process of blood regeneration. Muir and Shaw Dunn (1915) suggest that this is because the renal epithelium is not concerned in the normal metabolism of iron as are the liver and spleen, and that the iron is deposited in the kidney as the result of haemoglobinaemia although it may occur in the absence of haemoglobinuria. In most of such haemolytic conditions there is evidence of active participation of the reticulo-endothelial system in the process with erythrophagocytosis in the littoral cells of the spleen and the Kupffer cells of the liver. It has been suggested that these cells break down the haemoglobin and that the iron pigment is secondarily absorbed by the liver cells. In the Marchiafava-Micheli syndrome there is no evidence of erythrophagocytosis and little to support the participation of the reticulo-endothelial system.

Baker and Dodds (1925) and Hjärre (1930) have shown that the injection of solutions of pure haemoglobin (free from erythrocyte stromata) has no deleterious effect on animals and that the haemoglobin is excreted unchanged in the urine. The former workers pointed out that this is true only so long as the urine is alkaline but if the urine becomes acid (pH 6.0) and there is an adequate concentration of chlorides, the haemoglobin will be precipitated in the collecting tubules in the form of a brown pigment which they regard as haematin. This granular deposit, if in sufficient amount, may produce intrarenal obstruction with anuria and this is generally considered to be the mechanism in post-transfusional urinary suppression and blackwater fever. The absence of urinary suppression in paroxysmal haemoglobinuria *e frigore* was explained by these authors as due to the small amount of haemoglobin excreted at any one time. In neither of the cases described was there any evidence of haematin deposition in the collecting tubules, but in Case 2 the urine was alkalinized while in Case 1 it was naturally alkaline. Muir and Young (1932) described the changes resulting from prolonged administration of stroma-free haemoglobin to rabbits. There was siderosis of the kidney with albuminous degeneration of the convoluted tubules but no storage of iron pigment in the Kupffer cells or hepatic cells. The haemoglobin was

excreted in the glomerular filtrate and was re-absorbed in part by the tubular epithelium where it was broken up with the partial retention of the iron pigment which was also excreted in the urine. They suggested that the liver cells had no capacity to break down haemoglobin and could store only iron liberated by breakdown of haemoglobin in the reticulo-endothelial system. Similar results have been obtained by Newman and Whipple (1932), using dogs. These observations are of considerable interest as the changes are similar to those found in the Marchiafava-Micheli syndrome.

We put forward the suggestion that the changes found in this disease are in keeping rather with humoral than with cellular haemolysis with liberation of haemoglobin into the circulation. The free haemoglobin resulting from erythronoclasia is excreted in the urine unchanged but some of it is broken down in the epithelial cells of the renal convoluted tubules with the deposition there of iron pigment which is in turn excreted in the urine. The stromata of the lysed erythrocytes form agglomerations in capillaries with the production of venous hyaline thrombi; these occur in the portal system where they give rise to hepatic zonal necrosis, and in the systemic circulation. The cause of this humoral haemolysis is unexplained.

#### *Summary*

1. Two cases of the Marchiafava-Micheli syndrome are described with full clinical and pathological findings.

2. The clinical picture is clear cut and the main features are moderate hepatomegaly, anaemia, haemoglobinaemia, paroxysmal nocturnal haemoglobinuria, persistent haemosiderinuria and a liability to venous thromboses.

3. The condition runs a protracted course and terminates in death. Splenectomy is without avail.

4. The chief morbid anatomical changes are thromboses of the central veins of the liver with zonal hepatic necroses, marked siderosis of the renal tubules and erythroblastic hyperplasia of the bone-marrow.

5. It is suggested that these pathological changes are the result of prolonged intravascular haemolysis.

6. The possibility that some obscure chronic acquired haemolytic anaemias may be *formes frustes* of the Marchiafava-Micheli Syndrome is suggested.

Our thanks are due to Dr. A. E. Gow and Professor L. J. Witts for permission to publish these cases and for much helpful advice and criticism.

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FIG. 1. Liver of Case 2. Haematoxylin and eosin. Central and mid-zonal necrosis with sinusoidal congestion

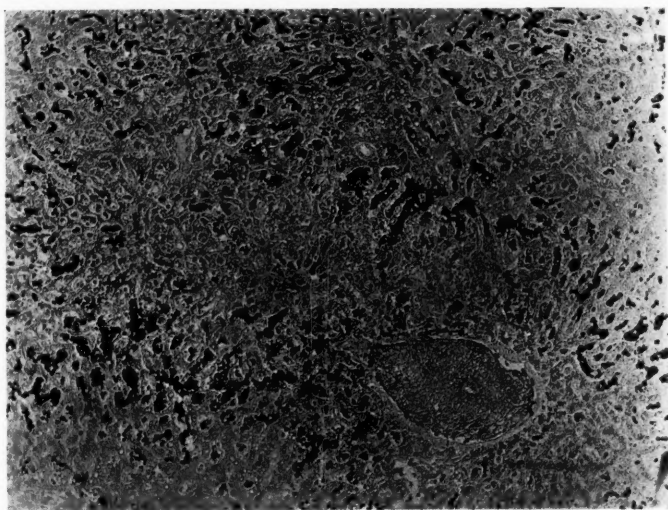


FIG. 2. Liver of Case 1. Lephne's stain. Agglomerations of erythrocytes in the dilated sinusoids and a fibrin thrombus in a branch of the hepatic vein



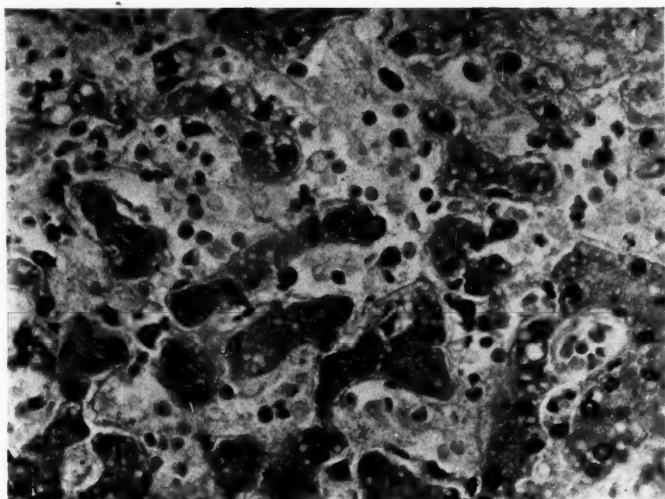


FIG. 3. Liver of Case 2. Iron haematoxylin and van Gieson. Normal erythrocytes (dark) and erythrocyte stromata (pale irregular circles) and fibrin threads in the sinusoids. Degenerate liver cells in the left-hand corner

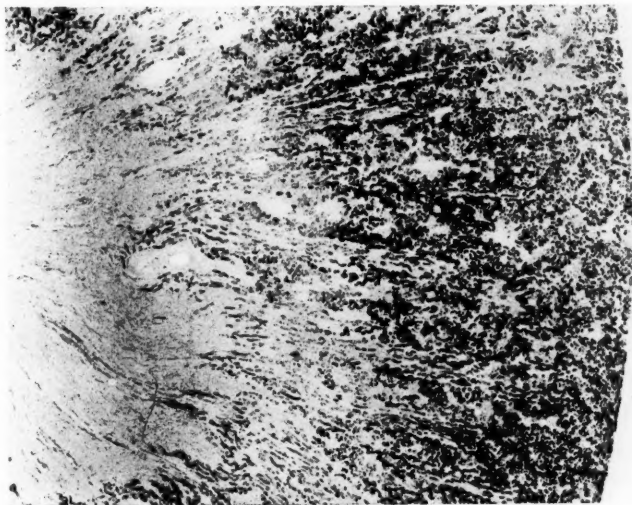


FIG. 4. Kidney of Case 2. Gömöri's stain for iron pigment. The iron pigment is chiefly in the convoluted tubules and loops of Henle; the collecting tubules contain none



## HYPERINSULINISM DUE TO A PANCREATIC ISLET ADENOMA<sup>1</sup>

By RUSSELL FRASER, W. S. MACLAY, AND S. A. MANN

(From the Unit, Maudsley Hospital, London)

With Plate 9

CLAUDE BERNARD was the first to demonstrate experimentally the existence of hypoglycaemia (1849) but it was not until 1910 that it was recognized clinically by Porges in a patient suffering from Addison's disease, and later by Joslin in 1927 in some diabetics being treated on low diets. Banting and others in 1921-2 recognized symptoms from insulin over-dosage and the syndrome of insulin hypoglycaemia soon became familiar. Spontaneous hypoglycaemia was first recognized as a symptom complex in 1924, and the term 'Hyperinsulinism' was applied to a group of cases reported by Seale Harris. The first operation for this condition, described by Wilder and others in 1927, was on a patient with carcinoma of the pancreas with secondary deposits in the liver from which insulin was extracted. The first successful removal of a pancreatic islet tumour for hyperinsulinism was reported by Howland and others in 1929. Since then pancreatic adenomata have been removed, with resultant cure of the hyperinsulinism, in over twenty reported cases. Spontaneous hypoglycaemia due to hyperinsulinism has also been described in association with carcinoma of the islets of Langerhans, in association with hyperplasia of the islets without tumour, and in other cases where the condition has been called functional hyperinsulinism as the condition has recovered without operative treatment, though these latter cases may depend on hyperplasia of the islets. Several islet adenomata have been found *post mortem* in cases where there had been no record of symptoms of hyperinsulinism (Whipple, 1935). Critical reviews of hypoglycaemia have been published by Gammon (1931), Harris (1932), Wauchope (1933), Wilder (1933), and Sigwald (1932), and of the adenomata of pancreatic islets by Whipple and Frantz (1935) and others.

This paper describes the case of a patient with a pancreatic islet adenoma whose symptoms were alleviated after removal of the tumour. There was good opportunity for close observation and investigation of the physical and mental state between and during many hypoglycaemic attacks, and also after operation. The case is reported in considerable detail as the number of such cases proved by operation and resulting cure is small (cf. 1, 2, 5, 7, 9, 13, 18, 20, 21, 23, 25, 30), and in the reports published it is only rarely that a full account of the mental as well as of the physical state is given.

*Case history.* The patient, a nurse aged 32, was admitted on 12.5.36 to the Maudsley Hospital, with a history of having suffered for seven months

<sup>1</sup> Received August 25, 1937.

from increasing general tiredness and attacks of dreaminess or unconsciousness. There was no history of mental or nervous illness in the family except that a paternal aunt had been in a mental hospital with schizophrenia. There were two siblings, both of whom were thin but otherwise healthy.

**Previous history.** As a child she was always thin and had frequent colds and bad chilblains; all her life she tired more easily than others and suffered from palpitation on exertion. Till the age of 20, she suffered from bilious attacks with headache and vomiting about once a year. She was always subject to frontal headaches at various times of the day and without evident cause, especially when she was tired. She was at school between the ages of 5 and 14 years and though she never liked it, was an average scholar. After a year of clerical training she took up nursing and has worked at four hospitals, with an intermission of two years due to her illness at the age of 20.

**Menstrual history.** Her periods started at 19, and were always irregular (6-8/21-28) and rather profuse. At these times she was irritable and suffered more from headache but was never laid up. The menses have not been affected by the present illness.

**Previous illnesses.** Apart from the tendencies to ill health mentioned above, she had had only two illnesses. At the age of 20 she began to suffer from various symptoms vaguely diagnosed as 'anaemia' which necessitated her giving up her work for two years. She was pale, tired all the time, suffered from frequent headaches, menorrhagia, increased frequency of periods, general uneasiness when upset, palpitations and dyspnoea on exertion. Apparently she made a good recovery as on returning to work she said she was feeling 'more fit than she had ever felt'.

At the age of 24 she had her first attack of psoriasis lasting three to four months. This recurred subsequently on three occasions each lasting several months. For the first attack she was advised to take a diet referred to later.

**Personality.** She has always been reserved, inclined to take offence, and has never made friends easily. Until recently she did a lot of cycling but did not take much other exercise outside her work. She was fond of reading and occasionally went to the cinema and theatre. She was very thorough and conscientious over her duties, particular about her clothes, and always took life seriously. Her mood was usually stable though she was readily tired and easily worried. She showed no excessive interest in her health. She took practically no alcohol.

**Diet.** As a child she was not allowed to eat between meals and was never fond of sweets or fat; she was often given tonics and foods to fatten her up. At the age of 24 she took a special diet for psoriasis consisting mostly of fruit, vegetables, and fat, with a minimum of starches and sugar but with full total caloric value. She took this for one year and subsequently during her attacks of psoriasis excepting the last one; between the attacks, except that she never ate sweet things, her diet was normal and she took the usual amount of other carbohydrate foods.

**History of present illness.** The present symptoms began when she had been eight months at a new post which was more responsible, and where the work seemed somewhat worrying and the atmosphere uncongenial. Four months previously her psoriasis had recurred and has persisted throughout this illness. Eight months before her admission she suffered from insomnia for about one month, only having two hours sleep on several nights in the week, and at the same time she began to feel irritable, worried and tired, especially in the morning. She felt that 'in a sense everyone was against her, and it

was not worth carrying on'. She would say to herself that she had to do it, but found this less and less attractive. She suffered from frequent sore throats and felt the cold severely, especially in her extremities. A typical day was as follows:—on waking she had a headache, was tired and hungry, but by breakfast-time had lost all her appetite. Though she never had any indigestion she would vomit about half an hour after breakfast on the mornings when she felt specially tired; but generally she felt better after breakfast. By 11 a.m. she would again begin to feel tired, and to find it difficult to keep her attention on her work, and would feel that she wanted a biscuit, which made her feel better. At this time, when trying to do the more exacting tasks, she often lapsed into a vacant dreamy state, in which she could not answer questions for two or three minutes, and in which she said that her mind seemed to be blank. By midday she would be ravenous, as was also the case occasionally in the evening. All these symptoms were more marked during menstruation.

During a menstrual period four months before admission she had her first severe attack, being found in the morning unconscious in bed. She regained consciousness in an hour, but did not completely recover for ten hours, during which she suffered from vomiting and headache. She was then in bed for a week without any abnormality being noticed. After this, she was constantly tired, depressed, and irritable, with a tendency to drowsy spells with headache on waking and during the course of the morning. She gradually lost her appetite, not feeling hungry even during the attacks, as she had originally done, and often vomited shortly after her meals. Subsequently, she had three similar severe attacks with unconsciousness lasting two hours to two days. During the menstrual period before her admission she was in a lethargic, depressed, irritable state, which culminated in another attack with unconsciousness lasting for five days despite tube-feeding three-hourly from the second day. Soon afterwards she was transferred to the Maudsley Hospital.

*Condition on admission* (12.5.36). She lay with a blank expression, showing little spontaneous talk, activity, or interest. Her appetite was poor, she slept heavily at night and was drowsy during the day. She answered questions in a dull monotonous voice only after a long pause, and looked suspicious. All her actions were very slow and tended to be clumsy. She denied feeling depressed, stating that she merely 'found herself terribly tired'; but she cried frequently and was irritable. Attention seemed possible only with great effort. There was no evidence of delusions, hallucinations, or compulsive phenomena. She was normally orientated. In sensorium tests she could repeat only five numerals forward and three backward, and she took three minutes to take serial 7's from 100, with six mistakes. She also made several mistakes in simple addition, multiplication, and subtraction. When shown these performances later she said 'It was not so much that I couldn't, but fed-upness', but it was clear to the observer that this was not an adequate explanation. She had difficulty in writing, and at times in remembering words, but the main trouble was in forming words with her pen; her speech was slightly slurred. She could give no explanation of her illness except that 'things had got on top of me'. These sensorium tests were repeated shortly before her operation, when her performance was much improved, so that the above results must be considered as partly due to her recent prolonged coma.

Physically, she was thin and of asthenic build; her weight, formerly 9 st. 12 lb., was 8 st. 12 lb.; height 5 ft. 7 in.; B.P. 130/85; P. 72; R. 20; there was never any pyrexia. There was widespread psoriasis of moderate degree.

Her complexion was pale. Her tonsils looked large and somewhat unhealthy. No other abnormal physical signs were discovered.

The following estimations were found to be relatively normal:

*Blood count.* Red cells  $4\frac{1}{2}$  millions per c.mm.; haemoglobin 12 gm. per 100 c.c.; leucocytes 5,400 per c.mm.; polymorphs 65 per cent., lymphocytes 30 per cent., eosinophils 1 per cent., and monocytes 4 per cent. (Following treatment with iron her haemoglobin returned to 13.2 gm. per 100 c.c.)

*Blood chemistry.* Urea N. 15 mg. per 100 c.c. (whole blood); cholesterol 153 mg. per 100 c.c. (whole blood); inorganic phosphate 3.8 mg. per 100 c.c. (serum); phosphatase 1.8 units per 100 c.c. (serum) (Bodansky); (these last two readings were taken in an attack); bicarbonate 60 vols. per 100 c.c. (plasma); chloride 358 mg. per 100 c.c. (plasma). W.R. and Kahn test negative.

In the spontaneous attacks observed it was found that administration of glucose orally, by nasal tube, or intravenously, restored her to normal. When starved for twelve hours she was found to be in one of her milder attacks of dreaminess and her blood-sugar to be 70 mg. per 100 c.c. After similar starvation on other mornings 5 units of insulin were injected intravenously, and on another occasion subcutaneously, with the production on each occasion of one of her severe attacks of complete unconsciousness, from which administration of glucose revived her rapidly as in the spontaneous ones. A detailed description of these attacks, with results of glucose tolerance and other metabolic tests will be given later in this paper.

The C.S.F. removed during an attack with coma had the following composition: sugar 42 mg. per 100 c.c.; urea N 14 mg. per 100 c.c.; NaCl 750 mg. per 100 c.c.; protein 25 mg. per 100 c.c.; cells under 1 per c.mm.

No abnormality of the liver was revealed by a radiograph of that area, or by a 50 gm. galactose tolerance test in which 2.4 gm. were excreted in the subsequent four hours (normal = under 3 gm.). The urine showed no abnormality at any stage of the twenty-four hours, not even acetoneuria, during the attacks. Radiographs of the skull to show the pituitary fossa revealed no abnormality. Her impedance angle (Brazier, 1934) was -18 and her B.M.R. after twelve hours starvation was -18 per cent., and -15 per cent. when this period of starvation was interrupted by giving glucose five hours before the test to prevent her being hypoglycaemic during it. These results were thought to exclude any significant thyroid dysfunction, which was in agreement with the clinical findings.

Thus in this patient, who suffered from persistent tiredness and depression with periodic attacks of clouding of consciousness, it was first found that the attacks represented spontaneous hypoglycaemia, since they could be terminated by feeding with glucose, could be induced by starvation or insulin, and were always associated with low blood-sugar levels. There was no evidence of significant defect in the diet during the period of onset, nor of renal glycosuria. Further the neurasthenic symptoms present between the attacks were not associated with any abnormal clinical signs which could be considered suggestive of hypocortico-adrenalism, pituitary disease, liver disease with storage defect, or any neuromuscular disease; so to account for all her symptoms a diagnosis was made of true hyperinsulinism, due either to hyperplasia or to neoplasm of the islets of Langerhans.

*Progress.* She was put on a high carbohydrate diet with meals at approximately two-hourly intervals from 6 a.m. to 10.30 p.m., making a total daily intake of C. 400 gm., P. 68 gm., F. 94 gm. It required continual attention from the nurses and effort on her part to persist with this, especially for

the morning feeds, when she often had to be roused to take her first drink. She gradually became less tired, anxious, and depressed—though never at any stage of her stay in hospital was she entirely free from these symptoms. In the morning she still had her minor attacks about once a week, generally related to lapses with a meal, or to vomiting after eating, and especially during her menses.

It was then decided to try the effect of a high fat diet (C. 100, P. 75, F. 250), together with insulin as advocated by John (1935). It was found impossible to give the full 20 units of insulin t.d.s. that he recommended, as a minor attack always came on during the morning if the full breakfast dose was given. She was given 10 units, half an hour after lunch and supper. Attacks became more frequent, occurring about twice weekly, and occasionally in the afternoon as well as in the morning; and her general lassitude, depression, and anxiety were more pronounced, especially about two and a half hours after meals. This observation bears out John's opinion that a failure to respond to such treatment may indicate a neoplastic basis for the hyperinsulinism. After a month's trial of this treatment it was abandoned, and the previous high carbohydrate diet was resumed, but with insulin as during the fat diet period. After a short period the insulin was omitted, with some resultant improvement in her condition. However, her general condition and the frequency in her attacks persisted much as in the earlier period with the high carbohydrate diet. She was then given benzedrine 10 mg. b.d. for a period of a month, which ameliorated her tiredness and depression somewhat. Then for a fortnight she was given ephedrine gr. i t.d.s., but she did not seem so well as without it. Throughout her stay in hospital her drowsiness in the morning tended to increase, and during the last two months she was given an extra drink of 25 gm. of glucose at 2.30 a.m. with, however, only partial relief of this symptom.

Thus it was possible by dietetic measures to maintain her in a condition of moderate activity, and she was up most of the day; she was drowsy in the morning, continuously tired and somewhat depressed, found difficulty in concentrating, and it was only with considerable effort that she kept to the dietetic requirements necessary to maintain even this state. She put on  $1\frac{1}{2}$  stone in weight during her stay. Apparently treatment had merely improved her general health and resistance to the basic abnormality, whereas the hyperinsulinism itself had perhaps progressed as shown by her diminished resistance to starvation, evident in the morning drowsiness and blood-sugar level (Fig. 1). This, in conjunction with the metabolic tests referred to later, confirmed the probability of a pancreatic tumour which had been suggested initially by the severity of her symptoms, and she was transferred to Hammersmith Hospital for laparotomy. Just before transfer her sensorium tests were repeated, when the results were found to be almost within normal limits. She said that she had gradually regained her writing ability, 'It was like learning again'. She remembered now seven digits forward and five backwards, took the serial 7's from 100 in two minutes, without any mistakes, and performed various tests well, though still rather slowly.

At Hammersmith Hospital she was under the care of Dr. R. S. Aitken, and twelve months after the onset of symptoms a laparotomy was performed by Prof. Grey Turner, under spinal anaesthesia, supplemented by a small amount of nitrous oxide and oxygen.

Through a transverse abdominal incision which divided both recti muscles, as described by Whipple and Pranz (1935), the pancreas was exposed. On

inspection there was nothing suggestive of pathological change, and it was only by palpation that a small nodule about the size of a pea was located, buried in the middle of the body of the gland, near its junction with the head. After its discovery a large vein was noticed over its surface. The pancreatic tissue was divided over the nodule, which was then carefully enucleated by blunt dissection. There was a little bleeding from the bed of

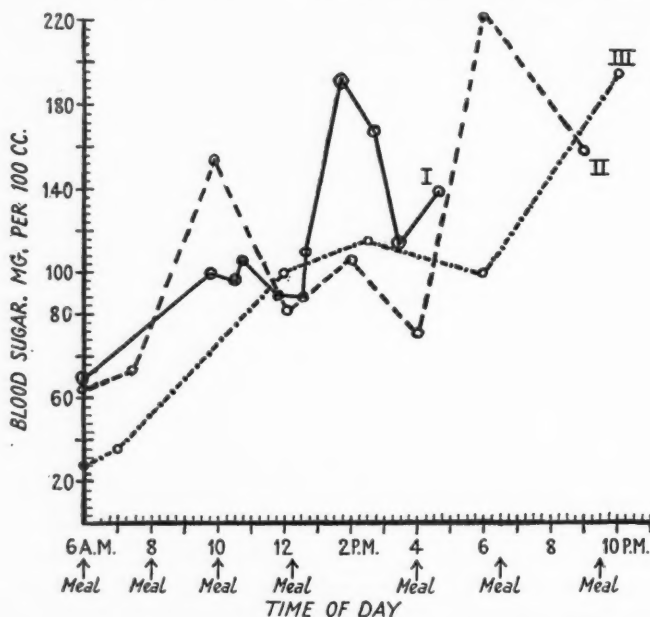


FIG. 1. Levels of blood-sugar throughout the day, at different periods of her illness.

— Curve I: 9.6.36: while receiving routine ward diet (meals not exactly as marked).

- - - Curve II: 5.8.36: after some weeks on high fat diet.

- . . . Curve III: 6.10.36: after some weeks on high carbohydrate diet with additional 2 a.m. feed. Note decreasing level of morning sample, but occurrence of high levels even in the last curve, though then only after the evening meal.

the tumour; this was easily controlled by drawing the edges together with a fine catgut stitch. After a careful search, to exclude the presence of another tumour, a small rubber tube,  $\frac{1}{4}$  inch in diameter, was inserted down to the pancreas, and the abdomen was closed.

The patient was not unduly upset as the result of the operative interference. She vomited slightly the first day, and for the first four days had severe abdominal pain, perhaps partly of pancreatic origin, and not merely from the incision.

About three days after the operation a colourless discharge was noticed coming from the tube. This was enough to soak part of the dressing but not to come through it. During the next few days it became more copious and caused some excoriation of the skin. Laboratory investigation showed that it was pancreatic secretion. By the end of ten days the discharge had so much diminished in amount that the tube was removed, after which the track promptly healed. There were no other complications, and the patient

was allowed out of bed three weeks after the operation. After that her surgical convalescence was entirely uneventful.

Three hours before the operation the patient had been given 50 gm. of glucose by mouth, but otherwise her pre-operative preparation was the usual one; her blood-sugar on return to the ward was 79 mg. per 100 c.c. She was then fed two-hourly almost entirely with drinks of milk or orange with

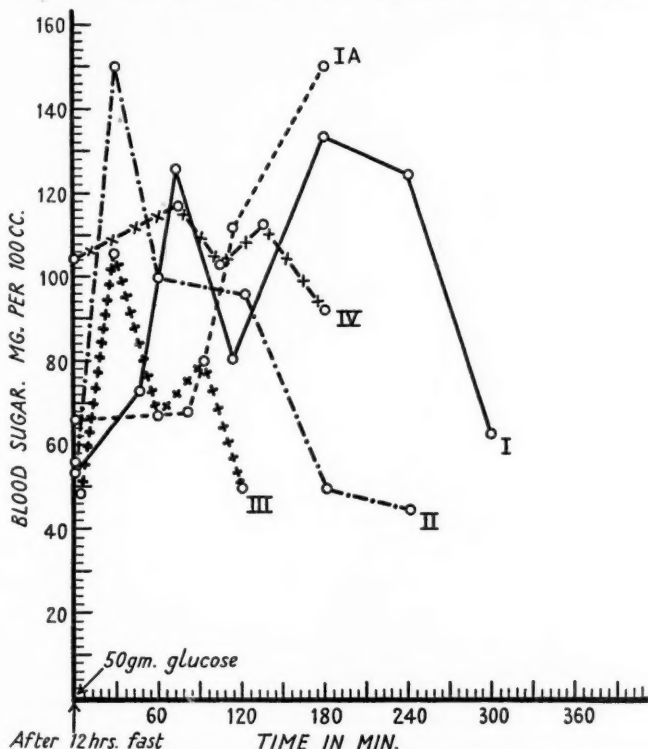


FIG. 2. Oral glucose tolerance tests: 50 gm. of glucose, after 12 hours starvation.

— — — — — Curve IA: 5.6.36; ordinary ward diet.

— — — — — Curve I: 34.6.36; ordinary ward diet.

- . . . . Curve II: 20.10.36; high carbohydrate diet, for previous week at least.

+ + + + + Curve III: 1.12.26; 18 days after operation: after week of same carbohydrate diet.

x — x — x — Curve IV: 10.5.27; 6 months after operation: ordinary hospital diet.

Note gradual transition from 'Plateau' type of curves I and IA, to rapid rise and fall type in curve II, following supervised and measured diet, though fasting levels are low in both types. Note also in post-operative curves persistence at first (curve III) of low fasting level (symptomless) and in the later one (curve IV) the high glucose tolerance ('plateau' curve), though a normal fasting level has been regained.

glucose, other additions being gradually made to her diet; her total carbohydrate intake was 100 gm. on the first day and 150–200 gm. daily for the next five days. From the sixth day she was given ordinary ward diet at the usual times. Her blood-sugar estimated daily just before her mid-day meal for the first week ranged about 100 mg. per 100 c.c., (84–164 except for one on the third day of 64 mg. per 100 c.c.); on the ninth and tenth days her

blood-sugars after twelve hours fasting were 67 and 76 mg. per 100 c.c., though at no stage of her post-operative course were there any symptoms resembling her previous attacks of hypoglycaemia. For some time after the operation she was irritable, capricious, and 'difficult to manage'—her behaviour before the illness had at times been rather similar. She started to get up on the fourteenth day, was discharged five weeks after her operation, and

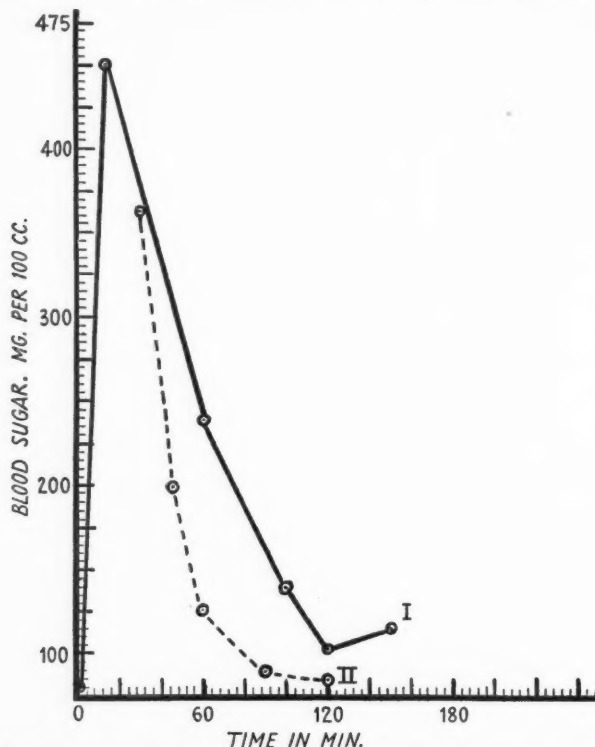


FIG. 3. *Intravenous glucose tolerance test* (as described by Fairley (1936)—50 gm. glucose in 600 c.c. aq. dest. given within 10 min.: 12 hours fasting). 19.7.36.

— — — — — Curve I: note apparently normal tolerance.  
 - - - - - Curve II: normal results as obtained by Fairley.

returned to her nursing duties as a sister three months after the operation. When seen five months after the operation she reported that she was free of all her previous symptoms and able to do a long day's work satisfactorily; clinical examination revealed no physical or psychiatric abnormality.

The results of a glucose tolerance test at this time are shown in Fig. 2, curve IV. It can be seen that the fasting level which was still low three weeks after operation (Fig. 2, curve III) is now normal, but that there is still an abnormally high tolerance for glucose—a rather unexpected feature which may alter later.

We are indebted to Dr. John Gray, Reader in Pathology at the British Postgraduate Medical School, for the following report on the pathology of the tumour and for the photographs of the tumour (macroscopic and microscopic) Plate 9, Figs. 12-14.

'Adenoma of islet of Langerhans. Macroscopically the growth is rounded, clearly encapsulated, and composed of a soft deeply congested tissue with apparently a fine connective tissue capsule. Measurements fresh— $1.0 \times 1.0 \times 0.75$  cm.; weight 0.65 gm. Histologically the structure is convincingly that of pancreatic islet tissue. Ordinary pancreatic glandular parenchyma could not be identified in the sections. The cells are fairly small, polyhedral,

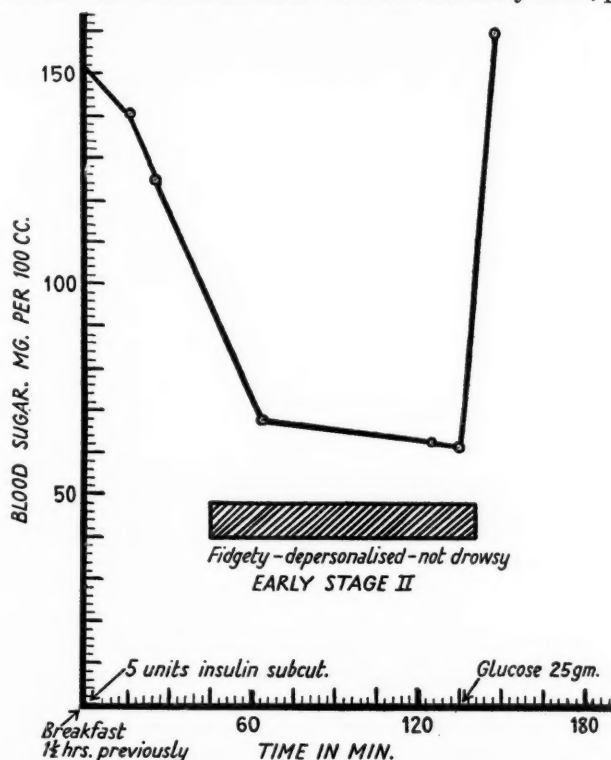


FIG. 4. Subcutaneous insulin tolerance test (5 units subcutaneously: no preliminary starvation). 30.6.36. Note recurrence of symptoms when blood-sugar falls below 70 mg. per 100 c.c.

with rounded nuclei and fair amounts of cytoplasm which stains moderately deeply with ordinary stains. Stroma is scanty and is mainly around the very numerous and frequently dilated capillaries. Some of the vessels are greatly dilated, thin-walled, and contain a fine structureless coagulum; it is not possible to be sure whether some of these are lymph vessels. The islet cells are in close apposition to one another. Sometimes they form fairly large solid groups, but there is a frequent and characteristic tendency for cells to arrange themselves around the capillaries, often in a single row and resembling a duct formation. In addition to the duct-like structure there are, right to the centre of the nodule, several well-formed true small pancreatic ducts, with a ring of collagen around each. A thin but definite fibrous capsule covers the whole nodule; a few groups of islet cells occur in the deeper part of this capsule. In no way do the appearances suggest malignancy.

'Granule stains. Most of the described granule methods were tried, two fixatives, formol-mercuric dichromate and osmic-formalin being employed. Both  $\alpha$  and  $\beta$  cells were present, but owing to under—or possibly over—fixation, the appearances were not uniform throughout the sections, and their relative proportions could not be estimated. The presence of pancreatic duct tissue has frequently been noted in these adenomata, and various ex-

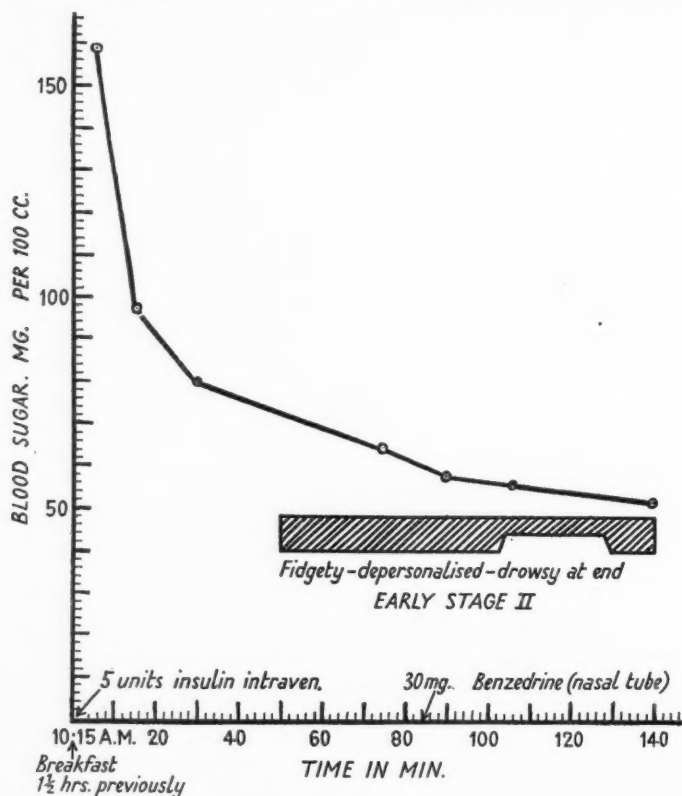


FIG. 5. Intravenous insulin tolerance test: 5 units intravenously after no preliminary starvation. 26.10.36. Note onset of symptoms after blood-sugar reaches 70 mg. per 100 c.c. and also slight transient relief of symptoms with oral benzedrine without alteration of the blood-sugar level.

planations given. It might be added that there does not seem to be anything in these sections to indicate a true blastomatous origin as against a process of localized hyperplasia.'

*Description of the attacks.* These tended to occur with special severity during her menses. Every spontaneous attack occurred after a period of some degree of starvation, usually a night's sleep; a small meal, insufficient to arrest an attack, sometimes seemed to exacerbate it, possibly by stimulating insulin secretion. The severe attacks were always the culmination of a two to three day period of increased general tiredness, depression, and headache, during which generally she also took less food. The usual sequence in a severe attack, as correlated from several, may be described in three stages:—

First stage—asthenia. On waking in the morning she felt drowsy, giddy, and had her usual headache; during the earlier part of her illness she felt hungry at this stage, but the hunger was soon replaced by nausea, and by vomiting if she ate anything. In the later period by the time she awoke she was more hypoglycaemic and so beyond the stage of feeling hunger. Seen during this stage she lay drowsily with little inclination to do anything,

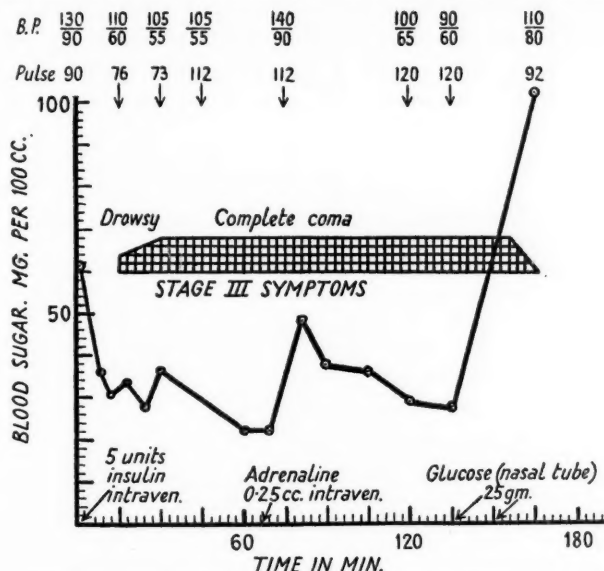


FIG. 6. Intravenous insulin tolerance test: 5 units of insulin intravenously after 12 hours preliminary starvation and 10 days high carbohydrate diet. 6.7.36. Note: mild symptoms present from the onset; onset of drowsiness 15 min. after injection; progress to complete coma within 40 min., persisting without any signs of spontaneous recovery till glucose administered, also slight and transient effect on blood-sugar by the intravenous adrenaline without any associated alteration of the coma.

and showed some annoyance and suspicion if spoken to or disturbed. Her skin was pale and dry, and her extremities cold. P. 70; B.P. 120/80. She conversed surprisingly well and admitted to the above symptoms, though the detection of any objective clinical abnormality, mental or physical, was frequently difficult, especially on some occasions in the later period of her illness, and yet in some of these her blood-sugar was as low as 28 mg. per 100 c.c.; it was usually between 70 and 50 mg. per 100 c.c. at this stage, never higher in the presence of these symptoms. If she got up, the above symptoms all became worse and by breakfast-time she felt unable to eat anything. Disinclination and feeling of inability to do anything gradually increased with the development of a dreamy feeling. She took about two to three hours to reach the next stage if no food or drugs were given.

Second stage—dreaminess and depersonalization. 'I felt absolutely unable to do anything—sit up or move; the more I tried the more hopeless it became.' She now felt dreamy and her body seemed 'rather lighter and different—as if I were here and not here'. Although she knew what she wanted to say, she had increasing difficulty in speaking; she also found increasing difficulty in thinking and following what was going on around

her, becoming readily confused. The results of physical examination during this stage were little different from the first stage; the state of her skin and extremities, pulse and blood pressure were unchanged, though sometimes the last was slightly reduced (110/75). There were, however, other clinically obvious abnormalities; sometimes, more especially during the earlier half of her illness, and for no obvious reason, she developed periods of apprehension, restlessness, muscular twitchings, choreiform movements, and an exacerbation of her irritability. On one occasion when in this stage she started a

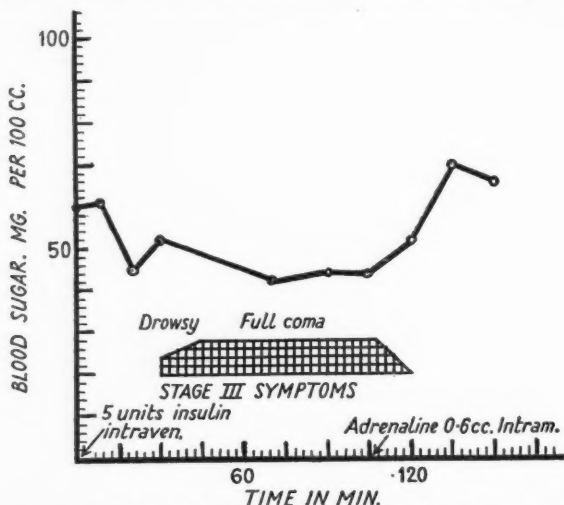


FIG. 7. Intravenous insulin tolerance test: 5 units of insulin intravenously after 12 hours starvation, and 10 days high fat diet. 17.8.36. Cf. with Fig. 6, and note the slower fall of the blood-sugar and onset of symptoms, but similar absence of spontaneous recovery till adrenaline injection roused her completely.

violent struggle with the nurse who brought her breakfast. She would perform various aimless actions unlike her usual behaviour—e.g. fiddling about with her bedclothes, wandering out of her room nude, &c. But she generally lay quiet and inactive. She could walk only with assistance, shuffling along, and occasionally walking right into the wall unless stopped. She responded to requests such as to show her tongue, slowly, sullenly, and reluctantly. In the later phases of this stage she was resistive to examination, and at times negativistic, e.g. closing her eyes more tightly when asked to open them. She seemed to refuse especially vigorously any offers of food, generally spitting out fluid placed in her mouth, or appearing to have real dysphagia if she tried to swallow it. There were now obvious mental abnormalities characterized by a varying combination of confusion, suspicious annoyance, apathy, and resistiveness. To simple remarks she replied slowly, with obvious difficulty of attention, and short answers. After two or three responses she would lapse into a vacant stare for some minutes and then return to her previous degree of attentiveness. She would insist that she was quite well and fit to return to her work, but was unable to perform even simple calculations. She could name common objects well—pen, paper, pencil, &c.—but she mixed the names of the doctors whom she knew at other times; when asked to read an address she mispronounced 'Maudsley' and lapsed into a dream-like state at the third line. She often showed perseverating tendencies,

e.g. one morning the answer to all questions was 'I don't know', although she really appeared to understand many of them. On another occasion it was 'I'm quite well' which she would reiterate. The blood-sugar was usually 60-45 mg. per 100 c.c. in this stage which generally lasted about half an hour before the next supervened.

Third stage—drowsiness and coma. She now began to feel an irresistible drowsiness, sometimes with a sensation of heat coming over her, and without any feeling of nervousness, soon passed into what seemed like sleep. She

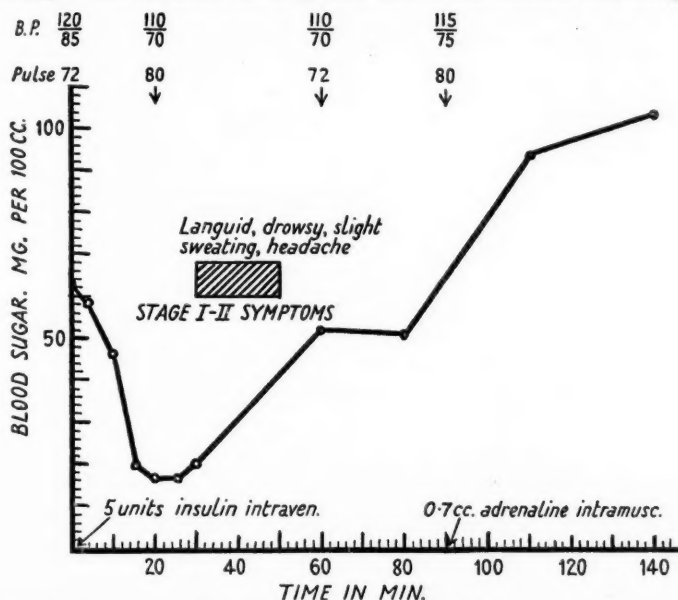


FIG. 8. Intravenous insulin tolerance test: 25 days after operation, 5 units of insulin intravenously, after 12 hours starvation, and a week of high carbohydrate diet. Cf. with Fig. 6, and note relative similarity of first 20 min. of both curves, but marked difference in the later parts; namely, a sharp spontaneous return to approximately fasting level well within 2 hours. Note that the symptoms were slight and transient and only occurred during the period following the maximum fall of blood-sugar. Note also relatively normal response of the blood-sugar to adrenaline. Cf. Fig. 9.

showed obvious abnormalities on physical examination; her skin was flushed and moist, though her extremities were still cold. B.P. was generally 90/60; P 80-90; R 20 and shallow. She usually showed slight generalized muscular rigidity of the extrapyramidal ('leadpipe') type, general increase of tendon reflexes, and *flexibilitas cerea*, all more marked in her arms; often one or both plantars were extensor. These motor signs appeared before complete loss of ability to answer questions. Gradually she would lose this ability, though still apparently understanding and able to obey commands. Later she seemed unable to understand what was going on about her, and when roused would look round in a bewildered manner. Finally any response even to painful stimuli was lost, and she lay in coma, atonic, with generalized decrease of tendon reflexes, flushed and sweating profusely all over. Her pulse was now 72; B.P. 90/55; R. 15 and more shallow. This complete unresponsive coma usually came on about  $\frac{3}{4}$  hour after the onset of the drowsiness. The stage of drowsiness was never seen before the blood-sugar

had fallen below 50 mg. per 100 c.c., and complete coma was generally observed when it was about 30 mg. per 100 c.c.; but sometimes, as already mentioned, only first-stage symptoms occurred with a blood-sugar of 28 mg. per 100 c.c. while on other occasions, referred to later, coma was seen with a blood-sugar of 45 mg. per 100 c.c.

In the five-day attack before her admission, during which this stage was

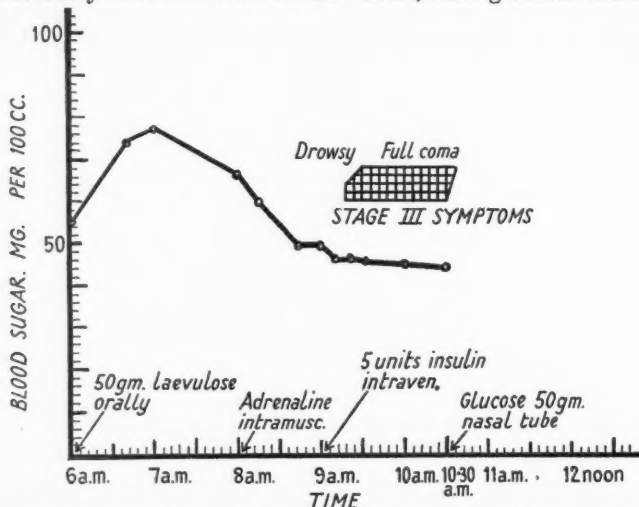


FIG. 9. Oral laevulose tolerance test: 50 gm. laevulose after 10 hours starvation, and period of high carbohydrate diet, followed by injections of adrenaline and insulin. 29.10.36. Note: normal laevulose tolerance test; absence of rise of blood-sugar within the hour following adrenaline (cf. Fig. 8). Severe coma following insulin at the same time after injection as in Fig. 6, but without significant effect on the blood-sugar. Absence of response during coma to intramuscular pituitrin. (Pituitrin 1 c.c. intramusc. at 10 a.m.)

prolonged, she showed spasms of rigidity in opisthotonos after being in coma for twelve hours; each spasm lasted about five minutes and was followed by a period of restlessness. She showed no such convulsions after three-hourly tube-feeding was instituted on the second day; but after each feed she was reported as 'calling out, restless and hysterical'—she remembered some of the later tube feedings and the subsequent restlessness: 'I knew I was fidgety, but couldn't explain why.' Till the fourth day she was incontinent and seemed to experience genuine dysphagia. By the fourth day she could say a few words and appeared to understand most things, though her condition was one of drowsiness broken by periods of restlessness after her feeds. By the fifth day she was much better except for nocturnal restlessness, difficulty with speaking and writing (mostly dysphasic), extreme depression and irritability, general physical and mental inefficiency and retardation. She took some weeks to regain her previous state between attacks.

Except for variation in the vasomotor symptoms and the inconstant incidence of periods of restlessness and involuntary movements, all attacks, spontaneous or induced, adhered closely to the above description. In the spontaneous attacks, both these variations seemed to depend on the rapidity of onset, which itself was related to the state of her health at the time, e.g. nutrition, degree of hyperinsulinism, number and severity of attacks for the previous few days. During the earlier phase of her illness when the

attacks came on more slowly, general flushing and sweating were seen sooner and were often associated with periods of restlessness and involuntary movements. Similarly a small breakfast insufficient really to dispel the hypoglycaemia, would be followed later by an attack of this character. In the attacks of more rapid onset the restlessness and involuntary movements were never observed and the flushing and sweating seen only in the deeper stage of coma.

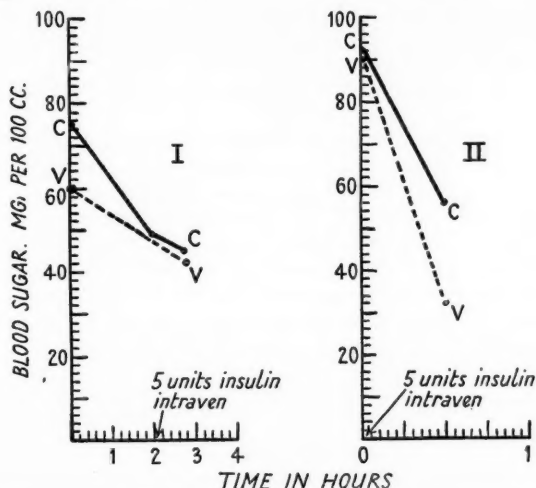


FIG. 10. *Capillary-venous differences* (observed during intravenous insulin tolerance tests). I. Before operation, during an attack with coma (29.10.36). II. 5 months after operation, during hypoglycaemia following a dose of insulin. Note the small difference seen in I during an attack of coma, compared with that in II (after operation) during hypoglycaemia, of approximately the same mean blood-sugar level.

Glucose, galactose, and laevulose, by nasal tube all roused her from the attacks. The dosage necessary and the time taken increased according to the severity and duration of the attack, as has generally been observed. For example, a minor attack was arrested in five minutes after 25 gm. of glucose (Fig. 4); a severe attack with unconsciousness lasting for two hours required 30 minutes after the administration of 50 gm. of glucose before it was arrested (Fig. 6); while one of similar severity in which unconsciousness had only lasted 40 minutes, responded to the same dose in 10 minutes. Ephedrine by nasal tube, or an injection of adrenaline also roused her completely in about the same time (Fig. 7), but did not raise the blood-sugar beyond 65 mg. per 100 c.c., and the recovery did not last long without further feeding. Benzadrine (Fig. 5) seemed to rouse her somewhat but the effect was transient and produced no alteration in her blood-sugar. Eucortone and pituitrin (Fig. 9) were ineffective for rousing her from coma, or for altering the blood-sugar.

#### Metabolic Data

Records of these data will be found in Figs. 1-10 and show several interesting features of the conditions. (All blood-sugars were by Calvert's (1925) modification of the Folin-Wu micro method on capillary blood, except where stated as venous.) The effect of the diet on the insulin tolerance (Figs. 5 and 6) is similar to that found in normal and diabetic subjects by

Himsworth (1934), namely, decreased sensitivity to insulin during the period on high fat and low carbohydrate diet; though, as mentioned, the attacks were most frequent then in the absence of sufficient carbohydrates to counterbalance the hyperinsulinism.

The glucose tolerance curve (Fig. 2, curve I) shortly after admission is of the 'plateau' type that Feinier (1935) has suggested is characteristic of hyperinsulinism. Similar curves have been found in sprue (Thaysen, 1935), hypopituitarism (Gardiner-Hill, 1925) and other conditions of malnutrition. Gammon (1931) points out the usual similarity of the glucose tolerance curves in hyperinsulinism to those normally found with low carbohydrate diets, which may be correlated with the abnormally high carbohydrate needs of these patients.

In Fig. 2, curve II, made under the same dietetic conditions as curve I, but at a period when the general nutrition had improved, is more nearly normal and tends towards the quickly rising and falling type. Similar curves showing normal fluctuations in the first two hours were found in cases of hyperinsulinism by Tedstrom (1932) in patients who were overweight and had been eating excessively. The daily blood-sugar curves (Fig. 1) show a similar change towards greater upward fluctuation as her nutrition improved and she gained  $1\frac{1}{2}$  stones in weight but later the increasing hyperinsulinism has tended to obliterate these rises except in the evening.

In Fig. 2, curves I and II show an excessive readiness of the blood-sugar to fall in the absence of food. It will be seen that this inability to compensate for short periods of starvation, which is the most characteristic feature of glucose tolerance tests in this condition, is best shown by the low fasting level, and by the low values of the third, fourth, or fifth hour specimens. Insulin may be injected at this fasting stage as a further method of testing these patients, noting especially any resulting symptoms and the persistence of these and of the blood-sugar fall (Figs. 4-9): perhaps most characteristic is the tendency of these 'hypoglycaemic' effects to remain undiminished for at least two hours unless treated, in contrast to the recuperative tendency seen in the post-operative curve (Fig. 8).

From these tests it was concluded that the sensitiveness to insulin as shown by the fall in the blood-sugar was normal, but that there was an abnormal tendency of the blood-sugar to fall spontaneously, and practically no tendency to spontaneous recovery from these low levels. This was taken to indicate some continuously acting abnormality, which could be well explained by a continuous excess of insulin in the tissues. The post-operative blood-sugar curves (Fig. 2, curves III and IV, and Fig. 8) show none of these manifestations though there is still moderate but symptomless fasting hypoglycaemia in the earlier ones.

An endeavour to throw some light on the oft-noted disparity between the blood-sugar level and the severity of hypoglycaemic symptoms was made by doing insulin tolerance tests: under varying conditions of starvation, 5 units of insulin were injected intravenously and the clinical state carefully noted and compared with the level of blood-sugar (Figs. 4-9). The results suggested the hypothesis that 'insulin-intoxication' may supervene when the blood-sugar falls below the critical level 70 mg. per 100 c.c., and the symptoms be dependent on this intoxication—an effect other than its action in lowering the tissue sugar concentration. While it was found that if the fall of blood-

sugar was rapid, these symptoms always occurred as soon as the level was about 70 mg. per 100 c.c. (Figs. 4 and 5) yet on other occasions when it had fallen slowly much lower levels were seen without recognizable symptoms—as mentioned in the description of the stages of the attacks. However, the intensity of these symptoms in relation to the blood-sugar level, did not appear to depend only on the rapidity of the fall of blood-sugar; in this respect Figs. 6, 7, and 9 should be noted. In the test recorded in Fig. 9 the initial clinical state was similar to that of the test recorded in Fig. 6, and equally marked 'hypoglycaemic' symptoms supervened at the same time after insulin injections, yet there was no demonstrable alteration in the blood-sugar. It seems unlikely that a fall of tissue sugar concentration, adequate to cause coma, could occur without any alteration of blood-sugar level, even although the adrenaline injected one hour previously to the insulin would still be active. Further, a similar test (Fig. 8) performed after her operation, showed a normal fall of blood-sugar, but only very slight and transient symptoms, in marked contrast to the severe and persistent symptoms shown in a pre-operative test (Fig. 6) in which the fall of blood-sugar after similar preparation was comparable. These results can all be explained by postulating an excess of insulin in her tissues before operation and presuming that insulin becomes toxic in the presence of low tissue glucose concentration. Sigwald (1932) uses the term 'glycopenic symptoms' to indicate their closer dependence on tissue than on blood-sugar; while it is generally agreed that such symptoms never occur in the presence of adequate tissue concentration, their incidence and severity after this concentration has fallen below its critical level (corresponding to a blood-sugar of 70 mg. per 100 c.c.) in this patient might depend on insulin concentration and its toxic effect under such conditions. It might even be suggested that the neurasthenic symptoms present between attacks are toxic effects from an excess of insulin in the presence of normal blood-sugar levels. The capillary venous difference in this patient (Fig. 10) shows reduced glucose utilization during a severe pre-operative hypoglycaemic attack, which suggests that one effect of the insulin intoxication is to interfere with the glucose utilization. Reference is made later to the relation of some of the less constant symptoms of hypoglycaemia to adrenaline secretion.

The intravenous glucose tolerance curve shows a rate of fall from high blood-sugar levels similar to, or at least not greater than, that found in normals by Fairley (1928). The relatively slight effect of the drugs normally raising the blood-sugar level is shown in Figs. 7 and 9. Adrenaline and ephedrine raised the blood-sugar only in hypoglycaemic attacks, and even then did not raise it to normal. This may be compared with the post-operative curve (Fig. 8) which showed a good response to adrenaline, indicating that these abnormalities might also be effects of a continuous excess of insulin in the body.

*Discussion*

The complete recovery of the patient following the removal of a pancreatic islet adenoma seems adequate proof that it was the cause of all her symptoms.

Some unusual features of hyperinsulinism were present in this case. Between the attacks, she suffered from a moderately severe neurasthenic state (weakness, irritability, depression, and insomnia) with slight lowering of B.M.R. and loss of weight. This state varied in severity during different periods of her illness, in accord with the frequency of the attacks, e.g. increase of both during the periods of high fat diet: this seems to indicate its close dependence on the effects of hyperinsulinism. Although such symptoms have been mentioned in several cases of hyperinsulinism, they have not been stressed: they appear to be rare in those patients of sthenic constitution who put on weight during the illness, but common in those of asthenic constitution.

Probably the presence of such symptoms between attacks can be correlated with some unusual features of her attacks, namely, the absence of a rise of blood-pressure at any stage, the late appearance of generalized flushing and sweating, and the relative rarity of apprehensiveness and hypermotility (either generalized restlessness or involuntary movement). All these features are generally seen during the earlier stages of hypoglycaemic attacks, and have often been described as cardinal features of the condition, whereas they seem to depend on the occurrence of some biochemical or other response initiated by the fall of blood-sugar. Such apparently secondary symptoms have been correlated (Sigwald, 1932) with the secretion of adrenaline shown experimentally to follow a fall of blood-sugar (Cori, 1931) though this may be only a partial explanation. Perhaps the asthenic constitution of this patient would account for the relative absence of such compensatory reactions, and her symptoms in an attack might, therefore, be more purely those of the glycopenic effects of hyperinsulinism. The evanescence of hunger in the syndrome of her attacks may also be related to her asthenic state. Thus there may be two main groups of symptoms in hypoglycaemia—those due to compensatory adrenaline secretion, and those due to tissue glycopenia, the latter being almost exclusively shown in the nervous system and possibly dependent on insulin intoxication. The signs and symptoms of the latter disturbance vary much in different patients but always include some disturbance of consciousness, the severity of which is a good indication of the degree of glycopenia. The evidence from this case strongly suggests that the chief symptoms of an attack might be ascribed to tissue glycopenia with consequent insulin intoxication, against which a blood-sugar level over 70 mg. per 100 c.c. protects the patient even in the presence of hyperinsulinism.

The mental state during a hypoglycaemic attack has the features of an intoxication with psychiatrically little to distinguish it from any other toxic condition. The exact clinical picture of an intoxication depends on many

factors which can be classified as (a) the amount, strength, speed of supply, and absorption of the toxic agent; (b) the bodily and psychic constitution; (c) the general health and mood of the patient at the onset of the attack. Some degree of disturbance of consciousness is the feature common to all stages of hypoglycaemic attacks, though it may be difficult to demonstrate at the onset. There is a progressive change from mild 'nervous' symptoms to a severer phase with confusion, abnormal behaviour, drowsiness and finally loss of consciousness. From a survey of other cases it would appear that the commonest psychiatric features in hypoglycaemic attacks before the onset of coma, are asthenia, clouding of consciousness with partial amnesia, drowsiness, and varying degrees of anxiety. Other abnormal features such as mania, depression, compulsions, fugues, deluded and hallucinatory states may complicate the picture as additions, but their presence seems to depend more on the individual personality.

It is interesting to note that the description of depersonalization along with feelings of apprehension and suspicion is strikingly similar to that of persons intoxicated with mescaline (Guttmann and Maclay, 1936). As in intoxications such as alcohol and mescaline, the early stages reveal abnormal reactions which can be understood and possibly anticipated in the light of the patient's previous personality, while profounder degrees of intoxication with clouding of consciousness show a much less individualized picture. In this patient's history there was evidence of asthenia and instability in times of stress, and such symptoms occur in mild attacks and to a lesser extent in the intervals between the attacks. Possibly it is significant in relation to the catatonic behaviour in her severe attacks that there were schizoid features in her personality such as asthenic bodily habitus, and character traits such as being reserved, easily offended and over-conscientious.

Feinier (1935) who used the increased susceptibility to starvation for diagnosis, found that some patients who were subsequently proved to be suffering from hyperinsulinism had to be starved for 48 hours before reproducing an attack. This tedious period of starvation can be avoided and metabolic data of diagnostic value acquired by giving 5 units of insulin intravenously at the end of twelve hours' starvation. If precautions are taken to avoid giving insulin to patients in a poor state of nutrition or with low blood-pressure, the procedure should be quite safe, so long as glucose is always at hand. For the type of case where this is contraindicated, the twelve hours' starvation should bring out any hypoglycaemic tendency. It is useful to combine this observation of the clinical effects of starvation and insulin with blood-sugar estimations; the latter, however, seem to be of much less diagnostic value than the changes observed clinically. The most useful times for taking samples of blood-sugar are at the end of twelve hours' fasting and then 30, 60, and 120 minutes after the intravenous insulin. Such insulin tolerance tests (Himsworth, 1934; Gray, 1935, and others), if they show a failure of the blood-sugar to return to the fasting level within 120 minutes, indicate a tendency to spontaneous hypoglycaemia, probably due to hyperinsulinism.

if the depression of blood-sugar by insulin is normal, as was found in this case.

The metabolic data from this patient have been interpreted as indicating a continuous excess of insulin in the tissues. The name Hyperinsulinism as initially suggested by Harris would, therefore, seem to be the most appropriate for conditions with spontaneous hypoglycaemia which show these metabolic features.

In conclusion we would like to thank Prof. Mapother for permission to publish this case. We wish also to express our indebtedness to Prof. Grey Turner and Dr. R. S. Aitken for their advice and help, and also to Dr. Gray, Dr. Mann and Mr. Partner for their assistance in doing the pathological and biochemical investigations.

### *Summary*

1. The clinical history, progress, and pathological findings are recorded of a patient in whom symptoms of neurasthenia with attacks of disturbed consciousness developed and were subsequently relieved by the removal of an adenoma of the islets of Langerhans.

2. Observation of the 'hypoglycaemic' attacks in this patient indicated a transition through three symptomatic stages described as asthenia, dreaminess with depersonalization, and finally, drowsiness culminating in coma. The psychiatric features of hyperinsulinism and 'hypoglycaemic' attacks are briefly discussed, and comment is made on the neurasthenic symptoms and some anomalous features of the attacks in this patient.

3. The results are given of glucose tolerance, insulin tolerance, and other tests of carbohydrate metabolism at various stages before and after operation. These indicated the presence, before operation, of a continuous excess of an insulin-like substance, shown best by the abnormal tendency of starvation or insulin to induce a persistent 'hypoglycaemic' attack with severe symptoms.

4. Observations were made during these tests on the correlation between the blood-sugar level and the severity of the symptoms, and are discussed. Reference is made to the possibility of an adrenaline response being the cause of some of the symptoms, and to the possible participation of insulin intoxication in the other effects of tissue glycopenia.

5. An insulin tolerance test after twelve hours' fasting obviated the necessity for the prolonged starvation otherwise required to induce an attack, and was the most useful procedure for demonstrating the presence of hyperinsulinism—reproducing a severe attack with no tendency to spontaneous recovery of blood-sugar level or symptoms within two hours.

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# HYPERINSULINISM DUE TO PANCREATIC ISLET ADENOMA 135

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FIG. 12. Macroscopic appearance of adenoma removed



FIG. 13. Microscopic section of adenoma removed.  $\times 270$   
(Stained with haematoxylin and eosin)

Shows the polyhedral cells in close apposition to one another, the scanty stroma, and thin-walled capillaries. The occasional duct-like structures are seen in a number of places



FIG. 14. Microscopic section of adenoma removed.  $\times 270$   
(Stained with haematoxylin and eosin.) Shows islet cells covering the capillaries



HAEMOLYTIC (SPHEROCYTIC) JAUNDICE IN THE ADULT<sup>1</sup>

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With Plates 10 and 11

THE type of acholuric jaundice described by Minkowski (1900) and later shown by Chauffard (1909) to be associated with an increased fragility of the red-blood cells was eventually subdivided into a congenital and an acquired group. The acquired type of Widal and his associates (1908) occurred in adults and differed from the congenital type in that it was clinically more severe, the spleen was not so prominently enlarged, the fragilities of the red cells were less constantly increased, and there was apparently no familial occurrence. Apart from these points, acquired haemolytic jaundice has figured in modern text-books of medicine as a rather vague and ill-defined syndrome whose existence has been repeatedly challenged. Tileston (1922), in reviewing the evidence then available, considered that all cases were examples of the 'congenital' form unless the onset occurred when the patients were over thirty years old or unless there was a definite disease present to which the haemolytic jaundice was a secondary manifestation. Dawson (1931) and Vaughan (1936) doubted the existence of an acquired form in any circumstances. The general opinion at the present time is that the so-called acquired haemolytic jaundice is not, as Meulengracht (1922) puts it, 'a nosological entity'. In these cases, the syndrome of jaundice with increased bilirubinaemia, absence of bile in the urine, and sometimes an enlarged spleen, is secondary to certain clinically and pathologically distinct diseases, such as Hodgkin's disease.

It seems clear, as emphasized by Thompson (1936), that the first symptoms of haemolytic jaundice may have their onset at any age, and although a history of affection of other members of the family is quite often obtainable, a considerable number of sporadic cases also occurs. But there is no doubt that when the disease first manifests itself in adult life it is liable to be more severe, with a more serious anaemia, and neither enlargement of the spleen nor increased fragility of the red cells may be so prominent. The increased fragility of the red cells in hypotonic saline has, since the work of Chauffard (1909), been regarded as pathognomonic of the disease. Nevertheless, some otherwise typical cases, usually adults, have been described in which the red cell fragilities seemed to be normal (Dawson, 1931; Gänsslen, 1922). Vaughan

(1936), however, thinks that accurate quantitative studies usually reveal some abnormality of red-cell fragility in all genuine cases of haemolytic jaundice. Since it is now becoming clear that the fragility test is subject to several errors (Whitby and Hynes, 1935), estimation by a quantitative technique is clearly desirable in anomalous cases, especially as Vaughan points out that abnormalities may occur within the normal range. There is, however, an anomaly of the red-blood cells which is at least equally, if not more pathognomonic of haemolytic jaundice than increased fragility; this is 'spherocytosis', i.e. the red cells, instead of presenting the usual form of a biconcave disk, tend to approximate to a spheroidal shape. The spherocytes show as dense microcytes in dried films or can be picked out in wet films (Gänsslen, 1925); their presence is also shown by a disproportionately large mean cell volume as compared with the mean cell diameter. This phenomenon of spherocytosis has been emphasized by Naegeli (1931), Meulengracht (1922), and Gänsslen (1925). Von Boros (1928, 1932) demonstrated quantitatively the increased thickness of the cells and Haden (1934) showed that spherocytosis could be correlated with increased fragility. Naegeli (1931), Gänsslen (1925), and others (10, 12, 18, 21) regard this production of spherocytes as the fundamental anomaly in this disease; as Thompson (1936) says 'the spherical microcytes . . . are as pathognomonic of this disease as are the sickle cells in sickle-cell anaemia'. Meulengracht (1922), however, regards their presence as a regeneration phenomenon and von Boros (1928) claims to have seen spherocytes in other conditions. Nevertheless, the view that the spherocytes are specific is becoming more secure, especially as spherocytosis or increased fragility persist after splenectomy (1, 5, 18), and Gänsslen (1922) has pointed out that the patients quite often present other physical abnormalities: if this view is correct the presence or absence of spherocytosis provides us with a criterion for distinguishing the less characteristic cases of haemolytic jaundice.

The morbid anatomy of the spleen has been well described by Turnbull (1936) as 'conspicuous narrow venous capillaries in a lake of blood', and is strikingly illustrated by Meulengracht (1922); both congenital and acquired types were said to show the same changes (13, 19). A different structure has been described in two cases: East (1933) described a case in which the splenic endothelium was found to be very hyperplastic and giant cells were present; the patient was a man of fifty-four who had a severe anaemia with high reticulocytosis and slightly increased fragility of the red cells: Kremer and Mason (1936) described the case of a woman, aged forty-six, with severe anaemia and slightly increased fragility in whose spleen numerous immature blood cells including haemocytoblasts were found.

The cases to be described here all showed a remarkable proliferation of histiocytes in the spleen without the characteristic overfilling with blood. They were adults and had severe anaemia, increased fragility of the red cells of varying degree, and showed spherocytosis. Splenectomy was carried out in all of them and, with the exception of one patient who died from post-

operative pneumonia, has been definitely beneficial, though the course has tended to be stormy without the brilliantly rapid recovery seen in haemolytic jaundice in younger patients.

#### *Case Records*

*Case 1.* A married woman, aged 32 years, was admitted to the Manchester Royal Infirmary on November 21, 1934. She had been complaining for four months of dizziness, loss of energy, and undue fatigue while her friends had noticed that she had a yellow colour. There was no dyspnoea, palpitation, rash, haemorrhages, or pruritus. Her appetite was normal and she had been free from digestive disturbances. Although the bowels were constipated the character of the motions had not changed. Micturition was normal but the urine had occasionally been dark-coloured. Menstruation had been normal until the last two periods when the flow became scanty. She had lost some weight. After her third pregnancy, two years previously, she had developed anaemia but was not yellow. She had never had any similar attacks previously and there was nothing relevant in her family or previous medical histories, although one brother was said to have been anaemic.

Examination revealed a fairly well-nourished brunette. She was strikingly icteric, almost golden-yellow in colour, with a malar flush. There was marked icterus of the conjunctivae and over the body surface generally. The temperature showed a fluctuating mild pyrexia, maximum 99° F.; pulse 96, regular and of good volume; weight 6 st. 5½ lb.; teeth fairly good. Throat and tonsils did not show anything unusual. In the abdomen, the tip of the spleen was easily palpable on inspiration, the liver was apparently of normal size, and no abnormal mass was found. There were no enlarged lymph glands and there were no noteworthy abnormalities in the other systems. Urine: specific gravity, 1020; acid reaction; contained a heavy deposit of urates and a trace of albumin, but no bile, blood pus, or casts. Blood count (22.11.34): red cells, 1,536,000 per c.mm.; haemoglobin, 40 per cent.; colour index, 1.33; white cells, 10,300 per c.mm.; polymorphonuclears, 90.5 per cent.; lymphocytes, 3.75 per cent.; monocytes 4.25 per cent.; eosinophils, 1.0 per cent.; basophils nil; myelocytes 0.5 per cent.; nucleated red cells, 2 per 100 white-blood cells. Anisocytosis was severe, poikilocytosis less marked; polychromasia common, punctate basophilia occasional; reticulocytes, 48 per cent.; platelets, 245,600 per c.mm. The Price-Jones curve (Fig. 1) showed megalocytosis of 52.4 per cent., mean diameter of red cells, 8.57 microns. The fragility of the red cells was definitely increased, the range being 0.60–0.38 per cent. NaCl. The van den Bergh reaction was directly positive; icterus index 26 units. The Wassermann reaction was negative. The blood belonged to Group A. Fractional gastric analysis gave free acid titres of: 0, 0, 2.3, 7.0, and 8.0 units in successive fifteen-minute samples. Radiological examinations of the skeleton were normal. In spite of the high reticulocytosis, the blood counts (Table I) rapidly fell and the patient's condition deteriorated with the onset of vomiting and increased pyrexia. A blood-transfusion (650 c.c.) was given on December 3 without undue reaction. A week later the blood count was lower than before and after another blood-transfusion (700 c.c.) on December 13, 1934, Mr. Graham Bryce removed the spleen, reporting at the same time that the liver appeared normal and the gall-bladder did not contain gall-stones. The spleen was dark and soft, weighed 400 gm., and showed no adhesions. After the operation the patient improved a little but the reticulocytes rose to a maximum of 87.3 per cent. (28.12.34)

and the platelets to 1,100,000 per c.mm. Her clinical condition again caused some anxiety with the falling blood counts (Table I) and further transfusions were given on December 31 (900 c.c.) and January 11, 1935 (600 c.c.). There was little improvement until late in January 1935 when both the clinical and the haematological conditions began to improve. There.

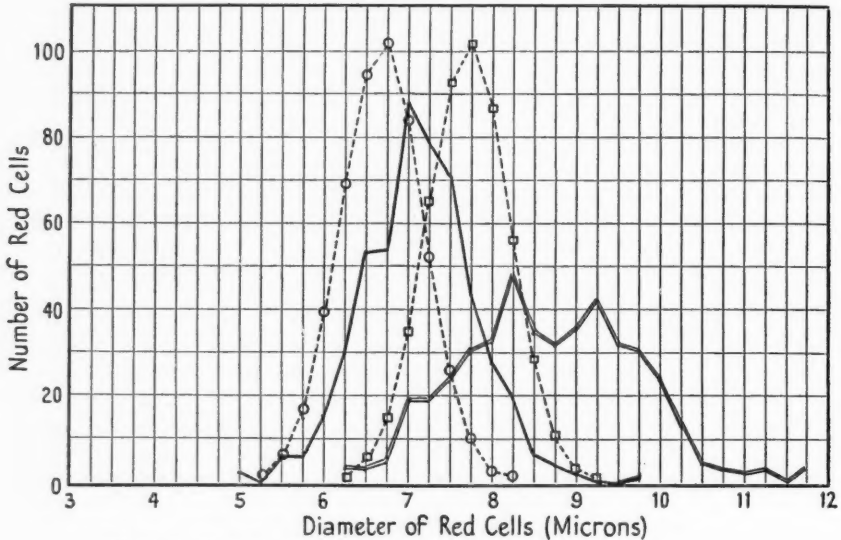


FIG. 1. Case 1. Price-Jones curves.

- -- ○ Ideal curve for smallest normal range.
- -- □ Ideal curve for largest normal range.
- — — — — Curve on 22.11.34.
- — — — — Curve on 23.9.37.

after progress was slow but steady, and treatment with intramuscular liver extracts, and later desiccated stomach powder (Pepsac) was given. She was discharged on March 30, 1935, when the red cells were 2,880,000 per c.mm., the haemoglobin, 67 per cent.; colour index, 1.15; white-blood cells, 16,200 per c.mm. She continued to improve, although it was some months before the blood count approached normal levels. Treatment with desiccated stomach powder has been maintained. On March 24, 1936, she had an acute follicular tonsillitis with false membrane and this was followed two days later by an attack of jaundice with some vomiting; bacteriological examination was negative, the van den Bergh reaction was a weak direct one, and the serum contained 13.5 units of bilirubin; she had recovered completely by April 9, 1936. There have been no further attacks since that time, and when last seen (29.9.37) she was still in very good health with the following blood findings: red cells, 3,830,000 per c.mm.; haemoglobin, 80 per cent.; colour index, 1.05; white cells, 6,600 per c.mm.; polymorphonuclears, 71.5 per cent.; lymphocytes, 20.5 per cent.; monocytes, 6.5 per cent.; eosinophils, 1.0 per cent.; basophils, 0.5 per cent.; nucleated red cells absent; reticulocytes, 2.8 per cent. The mean red cell volume was 106 c.microns; the mean cell diameter, 7.12 microns, with megalocytosis, 0.2 per cent., and microcytosis, 0.4 per cent. (Fig. 1). The red-cell fragility was still somewhat increased.

*Histology of the Spleen (Plate 10, Fig. 4).*

The pulp was noticeably cellular but not congested. There were great numbers of large pale cells with large vesicular nuclei and scanty cytoplasm; these cells were often collected in groups; they seemed to be of the splenic histiocyte type described by McMichael (1934). Many polymorphonuclear cells and lymphocytes were also present, but myelocytes and nucleated red

TABLE I

Date	Red cells 10 <sup>6</sup> per c.mm.	Hb. per cent.	Colour index	White cells per c.mm.	Nucl. red cells per 100 W.B.C.	Retics. per cent.	Treatment
<i>1934</i>							
22 Nov.	1.536	40	1.33	10,300	4	48	—
27 "	1.216	30	1.26	9,000	3	45.5	—
4 Dec.	2.488	50	1.00	5,200	—	43	Transfusion
11 "	1.064	22	1.01	9,600	8	43	—
13 "	—	—	—	—	—	63	Splenectomy
18 "	2.320	59	1.28	9,400	0	49.5	—
29 "	1.160	28	1.22	11,400	17	77	—
<i>1935</i>							
4 Jan.	1.856	40	1.11	11,600	9	43.5	Transfusion
11 "	1.048	28	1.40	19,400	26	53	Transfusion
18 "	0.752	20	1.43	18,000	300	62	—
25 "	1.416	30	1.29	8,600	9	48	Im. liver
4 Feb.	1.692	42	1.30	7,000	3	46.5	Des. stomach
18 "	2.512	52	1.04	9,400	0	16.3	" "
5 Mar.	2.592	60	1.11	8,400	1	32	" "
19 "	2.890	66	1.17	6,000	0	12	" "
25 Apr.	3.328	78	1.18	9,200	—	11	" "
23 May	3.800	83	1.08	6,200	—	8	" "
4 July	3.950	73	0.91	10,600	—	2.4	" "
29 Aug.	4.740	79	0.84	6,000	—	3.7	" "
14 Nov.	4.166	93	1.11	7,400	—	—	" "
<i>1936</i>							
30 Jan.	4.240	80	0.95	7,000	—	—	" "
26 Mar.	3.870	76	0.98	19,600	0	—	" "
21 May	3.310	78	1.19	4,800	—	—	" "
23 July	3.750	88	1.17	3,800	—	—	" "
10 Sept.	4.010	82	1.02	6,000	—	—	" "
17 Dec.	4.090	90	1.10	7,600	—	—	" "
<i>1937</i>							
28 Jan.	3.270	82	1.24	9,200	0	—	" "
11 Mar.	3.680	88	1.19	7,200	—	—	" "
6 May	4.000	80	1.00	6,200	—	—	" "
8 July	3.830	81	1.06	10,000	0	—	" "
23 Sept.	3.830	80	1.05	6,600	0	2.8	" "

cells were scanty. The sinuses were well-defined and rather dilated. There was no excessive fibrosis. The Malpighian bodies were prominent and often had pale hyperplastic centres.

*Case 2.* A married woman, aged 57 years, was admitted to the Manchester Royal Infirmary on December 17, 1936. Twelve months previously she began to notice loss of energy, attacks of palpitation and dyspnoea induced by exertion, and loss of weight. These symptoms became steadily worse,

and for the five weeks prior to admission she had been confined to her bed. It had been noticed that she was becoming increasingly pale and yellow—sometimes bluish in colour. Latterly she complained of some aching prae-cordial pain, and dyspnoea even while in bed. Her appetite was poor, flatulence had been marked, the bowels were regular. There was no abdominal pain, indigestion, or soreness of the tongue, but vomiting had been troublesome for a week. Some vertigo and deterioration of vision had occurred, while slight paraesthesiae in the hands and feet had been experienced. No

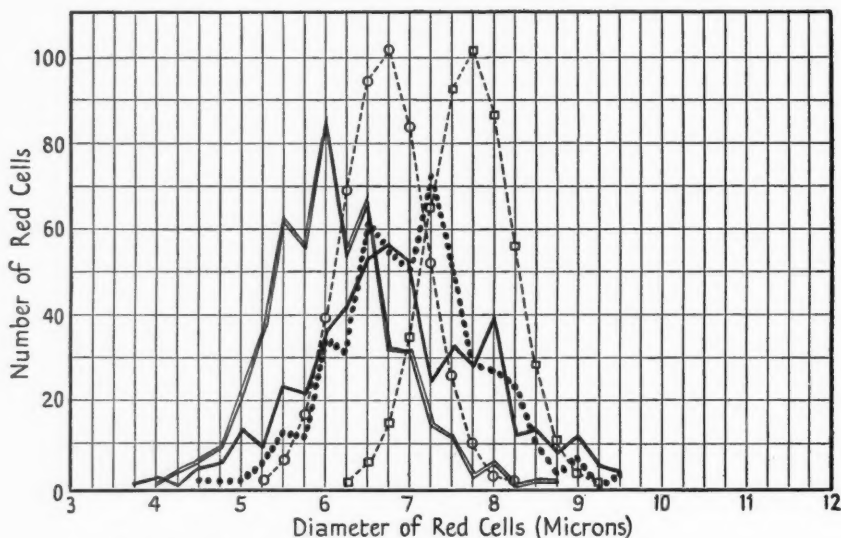


FIG. 2. Price-Jones Curves.

- - - - ○ Ideal curve for smallest normal range.
- - - - □ Ideal curve for largest normal range.
- • • • • Curve for Case 3.
- — — — — Curve for Case 4.

haemorrhages were reported and there was nothing of note in the previous medical and family histories.

On examination she was seen to be pale and had a markedly yellow colour with a malar flush; loss of weight was evident and she was noticeably dyspnoeic. Pulse, 112, regular, fair volume; temperature normal; teeth artificial. Tongue clean and smooth. Throat and tonsils, nothing of note. In the abdomen a firm, smooth and tender spleen was palpable two inches below the costal margin; the liver was not enlarged and there were no abdominal masses, or enlargement of the lymph glands. The heart was not enlarged and there were no murmurs; blood pressure 110/65. The lungs appeared to be normal. The pupils were equal and reacted normally, but the fundi showed some temporal pallor. The tendon reflexes were present and equal, and there were no objective sensory abnormalities. Urine: specific gravity, 1022; acid reaction; contained a trace of albumin but no other pathological constituent. The Wassermann reaction was negative. Van den Bergh reaction was direct delayed; the blood contained 2.0 units of bilirubin. Fractional gastric analysis showed that free acid was present

in the following titres:—0, 0, 2.5, 9.3, 14.0, and 13.0 units in successive fifteen-minute samples. The fragility of the red cells was definitely abnormal, the range being 0.65–0.40 per cent. NaCl (Whitby and Hyne's method, see Fig. 3). Blood count (18.12.36): red cells, 1,170,000 per c.mm.; haemoglobin, 25 per cent.; colour index, 1.13; white cells, 2,600 per c.mm.; polymorphonuclears, 68.5 per cent.; lymphocytes, 27.5 per cent.; monocytes, 2.0 per cent.; eosinophils, 1.5 per cent.; Türk cells, 0.5 per cent.; nucleated red cells, 17 per 100 white-blood-cells; reticulocytes, 6.5 per cent.; anisocytosis and poikilocytosis marked; platelets scanty. The Price-Jones curve (Fig. 2) showed a mean red cell diameter of 6.84 microns with megalocytosis 2 per cent. and microcytosis 12 per cent. The mean cell volume was 102 c.microns. The blood belonged to Group AB. The blood counts fell rapidly (Table II) and blood-transfusions (500 and 600 c.c.) were given on December 24, 1936, and January 3, 1937, respectively without any untoward reactions. The clinical and pathological findings strongly suggested that the patient had a chronic haemolytic anaemia and, from previous experience, we felt that splenectomy was advisable. Since her clinical condition was so poor we decided to give X-ray therapy a trial in the hope of obtaining some improvement. The blood counts, however, continued to fall steadily and a further transfusion had to be given on January 27, 1937. On February 1 the white cells were only 800 per c.mm., and the platelets, 72,400 per c.mm., suggesting that exhaustion of the bone-marrow was imminent. An intravenous blood-drip transfusion was commenced immediately and splenectomy was performed next day by Mr. Graham Bryce. The spleen was fairly large (700 gm.) but there were only a few slight adhesions and it was easily removed; there were no gall-stones in the gall-bladder and the liver appeared normal. Recovery was slow and complicated by thromboses of the deep veins of both legs, accompanied by pyrexia; at this point the platelet count had risen to 800,000 per c.mm. Six weeks after the operation the temperature had settled and the thromboses were disappearing satisfactorily. The platelet count, however, continued to rise, eventually reaching a maximum of 2,660,000 per c.mm. No more thromboses occurred until the end of May, 1937 when the superficial veins of the left leg and some of the intra-abdominal veins were involved while the veins over the right thigh were affected in the beginning of July, 1937. Throughout the whole of this period the platelet counts remained about 1,500,000 per c.mm. The blood counts showed slow but steady improvement and no further transfusions were required. Her general condition has also greatly improved, and she has been able to return home. The last blood count (3.9.37) showed:—red cells, 2,850,000 per c.mm.; haemoglobin, 72 per cent.; colour index, 1.24; white cells, 4,300 per c.mm.; polymorphonuclears, 57.5 per cent.; lymphocytes, 32 per cent.; monocytes, 6.5 per cent.; eosinophils, 0.5 per cent.; basophils, 0.5 per cent.; myelocytes, 3.0 per cent.; nucleated red cells, 26 per 100 white-blood cells; reticulocytes, 3.8 per cent.; platelets, 881,000 per c.mm. A striking feature in this case was the extremely high level of the platelet counts which persisted for many months after splenectomy; so far as we know, these are the highest platelet counts on record.

#### *Histology of the Spleen (Plate 11, Figs. 5 and 6).*

The spleen was cellular with no increase of connective tissue. The Malpighian bodies were rather small. The sinuses were noticeably dilated. The cells in the pulp were remarkable for the predominance of large cells with pale vesicular nuclei and scanty rather dark-staining cytoplasm; these

cells were often gathered in groups of five or more cells, some of them were in mitosis; some could be found in the dilated sinuses. Granular leucocytes, myelocytes and polymorphonuclears, and normoblasts were scattered in small numbers throughout the pulp, but there were no definite areas of 'myeloid metaplasia'. Red cells were notably scanty.

TABLE II

Date	Red cells 10 <sup>6</sup> per c.mm.	Hb. per cent.	Colour index	White cells per c.mm.	Nucl. red cells per 100 W.B.C.	Retics. per cent.	Platelets* per c.mm.	Treatment
<i>1936</i>								
18 Dec.	1.170	25	1.13	2,600	17	6.5	—	
24 "	0.784	19	1.22	2,800	15	10.6	—	Transfusion
31 "	0.928	23	1.24	1,600	2	4.6	—	Transfusion
<i>1937</i>								
5 Jan.	1.784	33	0.98	3,000	3.5	3.4	—	—
14 "	1.660	30	0.93	1,800	—	2.1	—	—
21 "	1.064	24	1.12	3,400	2	5.8	—	X-rays
28 "	1.336	27	1.01	2,200	3	2.4	—	Transfusion
1 Feb.	1.032	20	0.98	800	—	1.9	72,800	Transfusion
2 "	1.992	32	0.80	1,600	—	0.5	—	Splenectomy
8 "	2.440	44	0.90	7,400	7	3.1	317,600	—
21 "	2.220	40	0.95	16,300	4	5.0	664,000	(Thromboses)
31 Mar.	2.486	51	1.02	8,600	0.5	0.5	2,154,005	—
16 Apr.	3.128	59	0.97	10,200	6	0.5	2,472,000	—
14 May	3.200	61	0.95	9,800	40	3.5	1,674,000	(Thromboses)
10 June	2.752	60	1.10	8,800	—	—	1,122,000	—
5 July	3.350	70	1.04	19,400	49	—	1,565,000	—
27 Aug.	2.932	74	1.28	8,000	25	4.6	920,000	—
3 Sept.	2.850	72	1.21	4,300	26	3.8	881,000	—

\* Platelets were counted daily after Feb. 2, 1937.

*Case 3.* An unmarried domestic servant, aged 27 years, was admitted to the Manchester Royal Infirmary on January 13, 1937. For two years she had been suffering from increasing dyspnoea, lassitude, and undue fatigue; she had also been troubled with recurrent septic lesions on both hands and the left big toe, requiring incision. In July 1936, she developed severe jaundice which persisted for several weeks and, eventually, towards the end of August she became sufficiently ill to be confined to bed. In November, she was admitted to the local hospital where two courses of intramuscular liver injections were given but without improvement. When admitted to the Infirmary, dyspnoea was marked, but the patient did not complain of palpitation, indigestion, flatulence, nausea, vomiting, haemorrhages, oedema, paraesthesiae, or cramps. Her appetite was poor, the bowels were regular, micturition was normal, there had been no haematuria, and menstruation was regular but scanty. Nothing of relevance could be elicited in the previous medical and family histories.

On examination she was seen to be a well-built young woman with a marked yellow colour of the skin and mucosae, the tongue was clean and smooth, teeth artificial, throat and tonsils appeared normal. Temperature, normal; pulse, regular, full, rate 80; weight, 9 st. 13 lb. In the abdomen the spleen was not palpable, the liver was not enlarged and no abnormal masses were found; there were no enlarged lymph glands. The heart was slightly enlarged, there were no murmurs; blood pressure 140/90. The lungs and the central nervous system were normal. Urine: specific gravity,

1018; acid reaction; there were no pathological constituents. Blood count (14.1.37): red cells, 1,472,000 per c.mm.; haemoglobin, 38 per cent.; colour index, 1.24; white cells, 4,600 per c.mm.; polymorphonuclears, 72.5 per cent.; lymphocytes, 21.5 per cent.; monocytes, 5.0 per cent.; eosinophils, 0.5 per cent.; basophils, 0.5 per cent.; aniso- and poikilocytosis marked; nucleated red cells absent; reticulocytes, 11.2 per cent. The

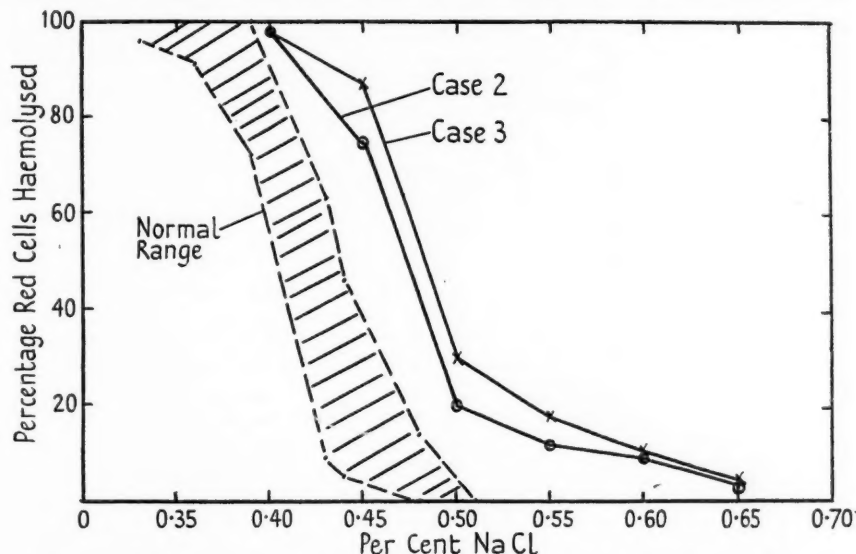


FIG. 3. Fragility of the red cells in Cases 2 and 3; method of Whitby and Hynes.

Price-Jones curve (Fig. 2) showed a mean cell diameter of 7.0 microns, with 1.2 per cent. megalocytosis and 3.2 per cent. microcytosis. The mean cell volume was 118 c.microns. The fragilities of the red cells were definitely increased, the range being from 0.65 to 0.35 per cent. NaCl (Whitby and Hyne's method, Fig. 3). Fractional gastric analysis showed the presence of free acid with titres of 0, 0, 3.0, 11.7, and 0 in successive fifteen-minute samples. The Wassermann reaction was negative. The van den Bergh test gave a direct delayed reaction; there were 5.8 units of bilirubin in the serum. The blood belonged to Group A. Bleeding time,  $3\frac{1}{2}$  min.; prothrombin time 9 min. The blood counts (Table III) showed some fluctuations but remained about the same level; there was a persistent reticulocytosis varying between 10 and 26 per cent. On February 4 the urine passed immediately after waking in the morning was found to be very dark coloured owing to haemoglobinuria, but during the day this cleared up somewhat, returning again the next morning. Bile was absent. This nocturnal haemoglobinuria continued with varying severity for six weeks. During this period the blood counts after an initial fall showed a fairly steady rise so that at the end of March the haemoglobin level was 58 per cent.; the reticulocytosis continued as before. In view of this recovery, and because we considered that the continued haemoglobinuria and rather high platelet count made conditions unsuitable for splenectomy, the patient was allowed to leave hospital for a time under observation. When she was readmitted on April 21, 1937, the urine showed only a trace of haemoglobin

and bile, but no red cells were seen microscopically; a week later the haemoglobinuria again became rather severe, and as her anaemia and the reticulocytosis continued, it was decided to proceed with the splenectomy, which was done by Professor J. Morley on May 13, 1937. The spleen was not very enlarged (170 gm.) and was easily removed. Within a few days of the operation the haemoglobinuria ceased. Recovery was uneventful. The

TABLE III

Date.	Red cells 10 <sup>6</sup> per c.mm.	Hb. per cent.	Colour index.	White cells per c.mm.	Retics. per cent.	Platelets. per c.mm.	Notes.
1937							
14 Jan.	1.472	38	1.24	4,600	11.2	—	—
21 "	1.512	38	1.28	3,200	10.1	—	—
4 Feb.	1.912	44	1.18	4,600	25.9	—	Haemoglobinuria
18 "	1.536	35	1.15	6,400	21.8	—	"
25 "	2.096	55	1.30	4,800	20.5	—	"
11 Mar.	2.440	60	1.22	4,400	16.1	—	"
24 "	2.148	58	1.34	3,400	20.3	456,000	"
23 Apr.	2.246	56	1.25	6,000	14.2	319,000	—
28 "	1.976	51	1.27	6,200	20.1	457,000	Haemoglobinuria
10 May	2.120	58	1.38	3,700	16.3	292,000	"
18 "	—	—	—	—	—	—	Splenectomy
21 "	2.400	60	1.30	6,000	15.0	608,000	—
28 "	2.100	58	1.38	5,400	6.0	592,000	—
4 June	2.510	66	1.30	3,200	6.8	435,000	—
8 Sept.	2.690	66	1.22	3,800	14.6	396,000	—

blood counts began to improve after about two weeks and the reticulocytosis subsided to more normal levels. She was discharged on June 7, 1937. She was seen again on September 8, 1937, and appeared to be very well although she was still somewhat jaundiced. There had not been any haemoglobinuria since discharge from hospital.

#### *Histology of the Spleen*

(Plate 11, Fig. 7). The pulp was cellular and did not show any excess of fibrous tissue. It was packed with large cells with large vesicular nuclei and usually pale, but sometimes basophilic cytoplasm resembling histiocytes; these cells were in rows and groups. The reticulum was prominent. Polymorphonuclears and myelocytes were seen in small numbers scattered throughout with a few normoblasts. Red cells were fairly numerous, but for the most part were seen only in clearly-defined channels. The Malpighian bodies were clear but rather small. Hyaline changes were evident in the arterioles.

*Case 4.* A motor mechanic, aged 25 years, was seen in the out-patient clinic on April 9, 1937, complaining of loss of energy, dyspnoea, and palpitation on exertion, headache, and dizziness. These symptoms had become steadily worse for four months, and palpitation began to occur with relatively slight exertion. Vomiting, chiefly of bile-stained fluid, had been present for two weeks. Increasing pallor and yellowness of the skin had been noticed, although the jaundice was only slight and of a creamy appearance. His appetite was poor, there was occasional flatulence and discomfort after food, the bowels were regular and the stools normal; some frequency of micturition had occurred, but the urine had appeared abnormal; his weight was steady. No haemorrhages or rashes had occurred. There was nothing of note in the

previous medical history and a careful inquiry into the family history was negative.

Examination revealed a well-built young man with a striking cream-yellow skin. Weight 9 st. 6 lb. Conjunctivae, pale. Tongue, clean and moist. Teeth fair. Throat and tonsils healthy. Pulse, 108, regular and rather collapsing. Temperature, some evening pyrexia up to 100° F. In the abdomen the liver was not enlarged, the spleen not palpable, and there were no abnormal masses. The heart, lungs, and central nervous system appeared to be normal. Blood pressure, 140/80. Urine, acid, no pathological constituents. Blood count (9.4.37): red cells, 2,080,000 per c.mm.; haemoglobin, 46 per cent.; colour index, 1.09; white cells, 4,800 per c.mm.; polymorphonuclears, 69 per cent.; lymphocytes, 29.5 per cent.; monocytes, 1 per cent.; eosinophils, 0.5 per cent.; basophils absent; nucleated red cells, 31 per 100 white-blood cells; marked aniso- and poikilocytosis. A diagnosis of haemolytic anaemia was made and he was admitted to hospital a week later for further investigation. The Wassermann reaction was negative. The van den Bergh test gave a delayed reaction; the serum contained 1.8 units of bilirubin. Fractional gastric analysis showed free acid in titres of 9.0, 9.5, 18.5, 26.5, 34.0, 35.0, and 36.0 units in successive fifteen-minute samples. Bacteriological examination of the throat and stools showed some haemolytic streptococci in the throat, but no unusual bacterial flora in the stools. The Price-Jones curve (Fig. 2) showed a mean cell diameter of 6.06 microns with microcytosis 44 per cent. and no megalocytosis. The mean cell volume was 110 c.microns. The fragility of the red cells was just beyond normal range, limits 0.50 to 0.35 per cent. NaCl. Reticulocytes at this time were 6 per cent. and a platelet count showed 99,000 per c.mm. The blood belonged to Group O. Biopsy of the sternal bone-marrow revealed marked hyperplasia of granulocytes, polymorphonuclears, myelocytes, and pro-myelocytes being numerous; normoblasts, mostly mature, were plentiful, no megaloblasts were seen. The blood counts fell rapidly (Table IV) and on April 28 a blood-transfusion (650 c.c.) was given without any reaction. A course of intramuscular liver injections was also given, but failed to arrest the further fall in the blood count. Splenectomy was considered advisable, and after another blood-transfusion, this was done by Professor J. Morley on June 15, 1937. The spleen was not very large (250 gm.) and was not adherent to other organs. There were no gall-stones and the liver appeared pale. Unfortunately, six days after the operation he developed a bilateral broncho-pneumonia which proved fatal.

#### *Histology of the Spleen.*

(Plate 11, Fig. 8). The Malpighian bodies were well marked and some showed hyperplastic centres. The pulp was cellular without excess of fibrous tissue. The sinuses were not particularly dilated, but in some parts their walls were very cellular. A notable feature was the large number of large cells with pale, vesicular nuclei and dark-staining cytoplasm; these were scattered throughout the pulp singly and in groups of up to eight cells. Some were in mitosis; some were detectable in the sinuses. The pulp was rather congested and erythrocytes were plentiful. Normoblasts and myelocytes were present in fair numbers, but neither they nor the normoblasts were concentrated in any special areas, they were uniformly distributed throughout the pulp. The reticulum was well marked.

The post-mortem examination (Dr. J. Davson) showed broncho-pneumonia

affecting the lower lobes of both lungs with early abscess formation. The liver (2,000 gm.) had a clear pattern and gave a strong iron reaction, microscopically there were some fatty changes and much free iron was found. The other organs were sufficiently normal to require no further comment.

TABLE IV

Date.	Red cells 10 <sup>6</sup> per c.mm.	Hb. per cent.	Colour index.	White cells per c.mm.	Nucl. red cells per 100 W.B.C.	Retics. per cent.	Platelets per c.mm.	Treatment.
1937								
9 Apr.	2.080	46	1.09	4,800	31	—	—	—
16 "	1.780	40	1.10	10,800	43	6	99,200	—
23 "	1.640	38	1.19	7,200	28	7	94,200	—
30 "	1.659	40	1.20	4,000	28	3	68,400	Transfusion
7 May	1.690	40	1.20	4,900	18	2	72,600	Im. liver
14 "	1.540	34	1.13	5,400	8	2.8	83,200	"
21 "	1.490	32	1.07	3,000	48	6	94,400	"
4 June	1.320	26	1.00	8,600	59	7.5	80,000	"
14 "	2.090	42	1.00	6,000	63	4	74,400	Transfusion
15 "	2.430	46	0.96	8,400	—	—	—	Splenectomy
21 "	2.040	39	0.97	19,400	125	3	162,500	—

We may summarize the significant features of the four cases described above. In the first place the patients were adults (aged 25, 27, 30, and 60 years), who suffered from a severe and progressive anaemia that failed to respond satisfactorily to various forms of anti-anaemic treatment or repeated blood-transfusions. The fragilities of the red-blood cells were definitely increased in the first three patients, but only slightly in the fourth. Case 1 had a megalocytic anaemia. On the other hand, Cases 2, 3, and 4 were of the microcytic type, although their mean cell volumes (102, 118, 110 c.mm.) were above the normal limits (82-92 c.mm.), indicating the presence of a definite spherocytosis, while dense spherocytes were seen in the stained blood films of all four patients. Following splenectomy in these patients, Cases 1 and 2 maintained a steady improvement after a somewhat stormy course, necessitating post-operative transfusions only in the first patient; Case 3 recovered much more rapidly, while Case 4 unfortunately died from post-operative pneumonia. All the patients were given blood-transfusions without undue reactions; the constant-drip method was found not to be essential. The condition of the spleen was of interest; only in Case 2 was it observed to be enlarged on palpation, but at operation moderate enlargement was also found in the other three patients. Histological examination revealed in all four spleens the presence of numerous large cells with pale vesicular nuclei and scanty or fairly abundant, usually dark-staining, cytoplasm corresponding to McMichael's (1934) description of histiocytes; some of the sinuses were dilated, and these cells could be found within their lumen; there was some proliferation of the cells of the sinus walls. There was no undue fibrosis, no 'myeloid metaplasia', and no overfilling of the pulp with blood. This is quite different from the histological features seen in typical haemolytic jaundice. Davidson (1932), in a miscellaneous group

of cases showing a megalocytic haemolytic anaemia, described two patients (Nos. 5 and 6) in which the histology of the spleen resembled that of our cases in some respects, but differed in presenting well-marked areas of myeloid metaplasia; the red-cell fragilities of both these patients were reported as normal, and no mention was made of spherocytosis. McMichael, who reported on the histology of the spleens, was of the opinion that the observed changes were secondary. The proliferation of histiocytes and the cellular increase in the sinus walls seen in our cases correspond to the changes cited by McMichael (1934) as being characteristic of the hyperplastic process in the human spleen.

Thus the question that arises is whether our cases represent (a) examples of true idiopathic haemolytic jaundice with an unusual hyperplastic reaction in the spleen, or (b) a primary disease of the spleen which has given rise to a haemolytic anaemia with acholuric jaundice. If we adopt the view of Meulengracht and von Boros that the spherocytosis and accompanying changes are regeneration phenomena, then the second alternative seems the more likely, especially as our patients, besides the histological changes in the spleen, presented other differences from typical haemolytic jaundice, such as the relatively small enlargement of the spleen, the severe and unremitting anaemia, and the relatively slow and sometimes incomplete recovery. On the other hand, if we accept the views of the majority of contemporary workers, and regard haemolytic jaundice as an inborn abnormality which manifests itself by the production of spheroidal erythrocytes, then the first alternative is more probable. The differences from typical haemolytic jaundice mentioned above are not vital (4, 18); cases have been reported in which the spleen was not prominently enlarged (4, 9), severe anaemias are known to occur and are sometimes megalocytic in character (6, 15), while the age of onset is no longer regarded as of great importance (9, 18). Our cases do not fall into Thompson's 'atypical group' (1936), in which spherocytosis was not demonstrable and splenectomy was not beneficial. The balance of the evidence suggests that our patients had haemolytic jaundice, or, as Krumbhaar (1936) prefers to name it, 'spherocytic jaundice', with an abnormal reaction in the spleen characterized by histiocyte proliferation. Splenectomy is just as surely indicated for these patients as for the typical cases, although recovery may be slower or less regular.

### *Summary*

1. Four adult patients suffering from a haemolytic jaundice are described. The condition is characterized by severe, progressive anaemia, moderately increased fragilities of the red cells, enlarged but often not palpable spleens, and definite spherocytosis.
2. The histological changes in the spleens, removed at operation, showed a remarkable proliferation of large pale cells with large vesicular nuclei and fairly scanty usually dark-staining cytoplasm, which were probably histiocytes;

the overfilling of the pulp with blood, normally characteristic of haemolytic jaundice, was absent.

3. Splenectomy was performed on all the patients; one died from post-operative complication, the other three recovered, but the course of recovery was slow in comparison to that seen in typical haemolytic jaundice.

4. The balance of evidence suggests that these patients had a form of haemolytic (spherocytic) jaundice characterized by an unusual histiocytic reaction in the spleen.

We have pleasure in expressing our thanks to the Honorary Physicians of the Manchester Royal Infirmary, who kindly placed these cases at our disposal, to Professor J. Morley and Mr. Graham Bryce for their skilful co-operation at the appropriate moments, and to Mr. Howat and Mr. Dacie for some technical assistance with the fragility determinations. The work has been supported by grants from the Medical Research Council and the Lady Tata Memorial Trust.

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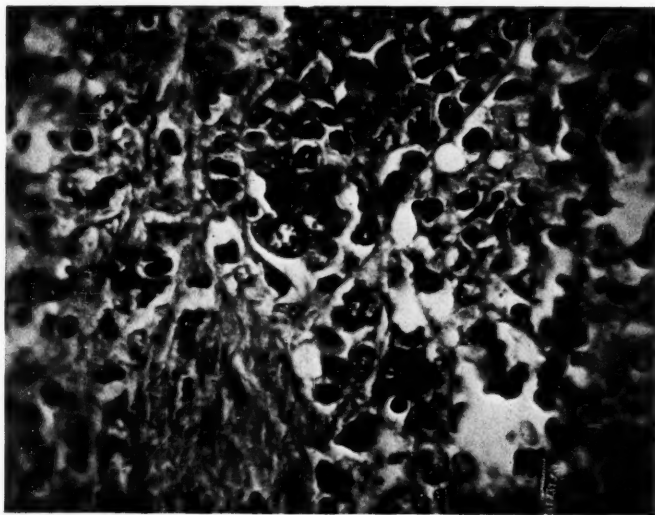


FIG. 4. Case 1; spleen,  $\times 750$ . (Jenner-Giemsa stain). The field shows the large histiocytes in the centre and the well-marked reticulum

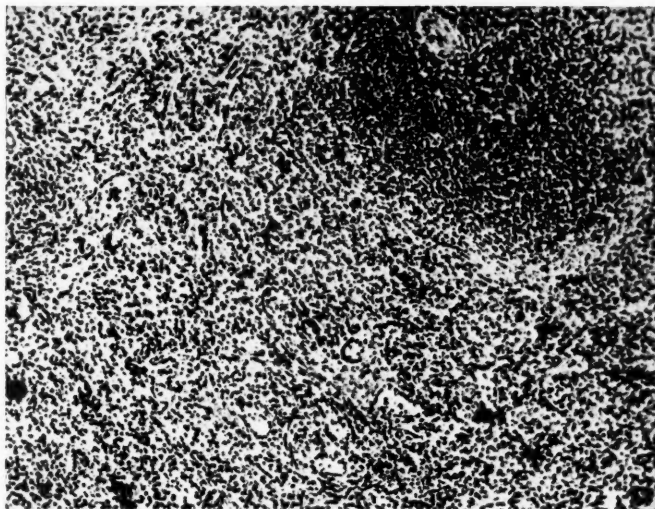


FIG. 5. Case 2; spleen,  $\times 90$ . (Haematoxylin and eosin). The pulp is cellular and well-marked groups of histiocytes can be plainly made out. Dilated sinuses are prominent, and their walls are cellular and clearly defined. A Malpighian body is partially visible in one corner of the field



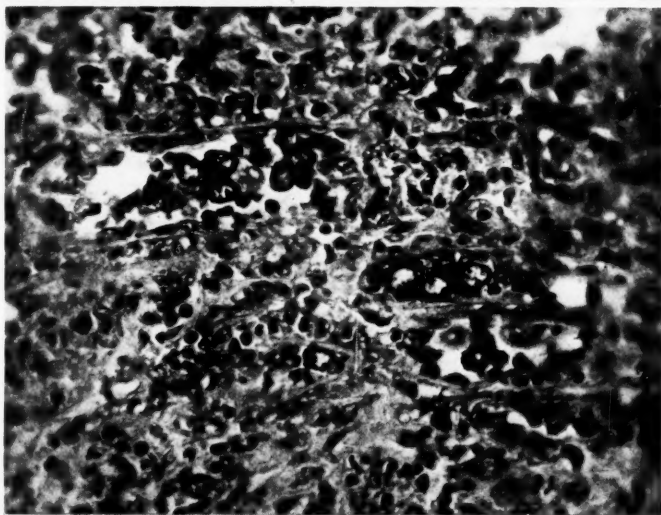


FIG. 6. Case 2; spleen,  $\times 500$ . (Jenner-Giemsa stain). In this figure the histiocytes can be seen within the lumen of sinuses; one or two are also present in the pulp. The walls of the sinuses are cellular and clearly-defined



FIG. 7. Case 3; spleen,  $\times 750$ . (Jenner-Giemsa stain). This figure shows the presence of histiocytes in the pulp and well-marked reticulum

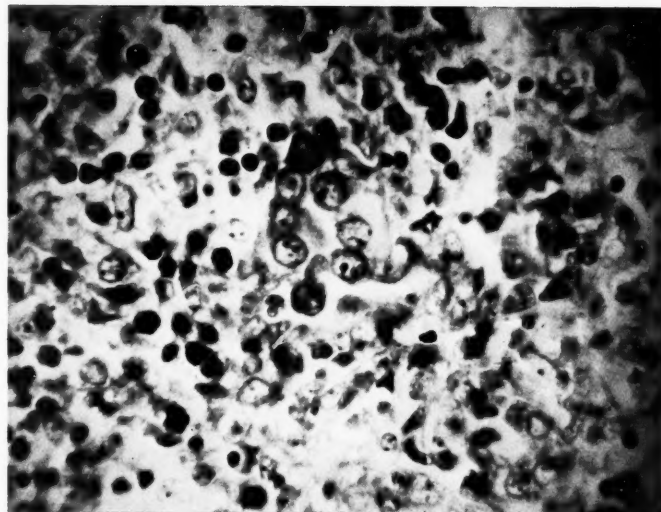
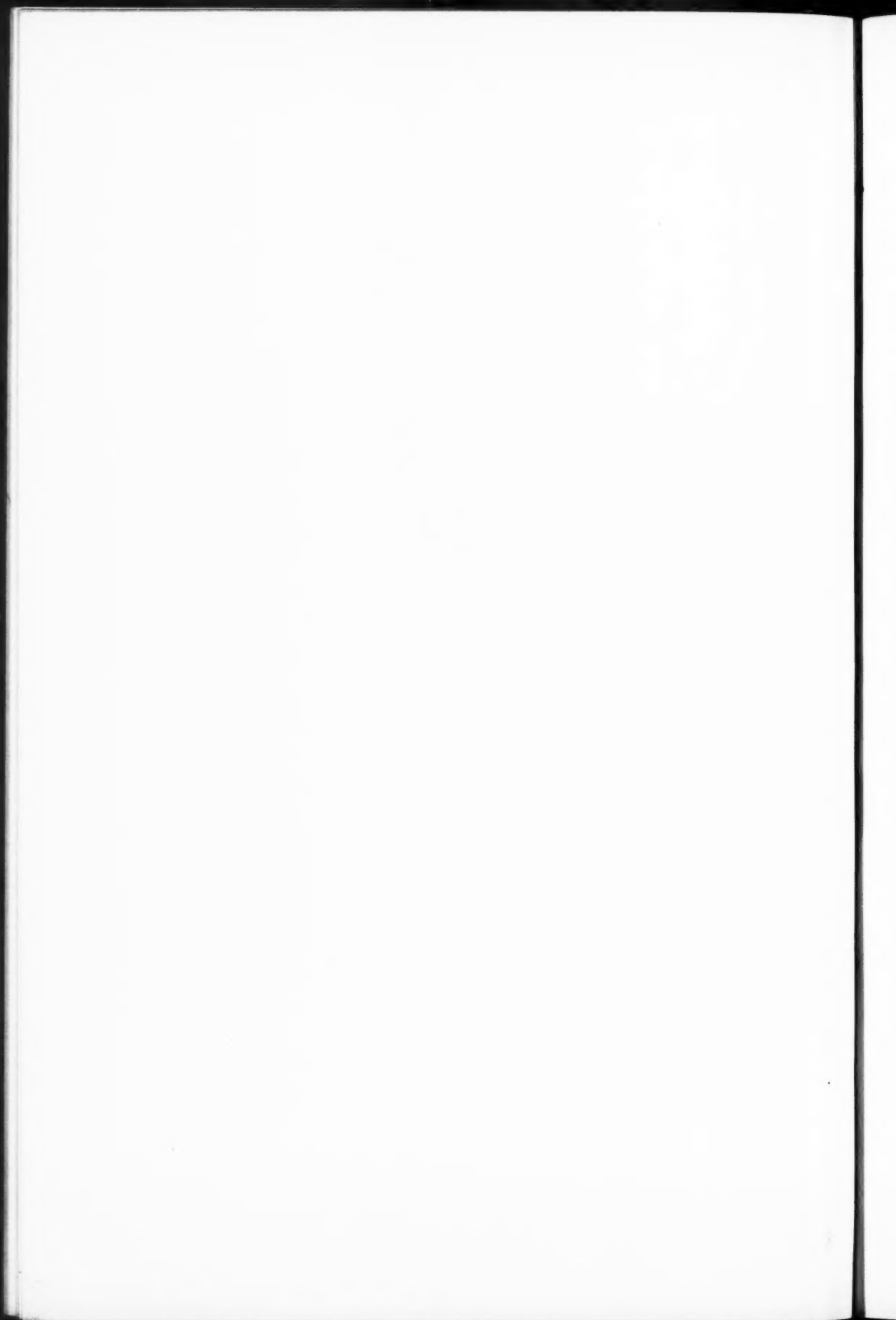


FIG. 8. Case 4; spleen,  $\times 750$ . (Jenner-Giemsa stain). A group of large histiocytes can be seen in the centre of the field and shows well the large vesicular nucleus and scanty cytoplasm



## THE ANTERIOR PITUITARY LOBE IN GRAVES' DISEASE AND IN MYXOEDEMA<sup>1</sup>

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### *Introduction*

SOME eight years have now passed since Loeb and Bassett (1929, 1930) first suggested that the active principle of the anterior lobe of the pituitary gland which is now known as the thyrotropic hormone might be of aetiological importance in exophthalmic goitre. This suggestion was the outcome of experiments in which they were able to show that suitable extracts of the anterior pituitary would produce hyperplasia of the thyroid in young guinea-pigs. In the same year, also, Aron (1929) independently called attention to the thyroid-stimulating properties of similar extracts. These early observations were speedily confirmed by other workers, and it has been firmly established that these stimulant effects are due to a definite entity which has been given the name 'thyrotropic hormone'. This hormone is readily extracted from the anterior lobe of the pituitary gland either by weak acid or by weak alkali. It has not as yet been obtained with certainty from any other organ of the body. The properties and physiological behaviour of this hormone have been studied by a large number of workers, and general agreement has been reached as to its main effects. It is apparently inactive when given by mouth, but when injected into a suitable experimental animal, such as the young guinea-pig, it produces enlargement and increased vascularity of the thyroid gland. The epithelium lining the vesicles of the gland becomes very hyperplastic, and the colloid softens and disappears. The functional activity of the gland is greatly stimulated and all the signs of increased thyroid secretion can be observed in the animal. Histologically the gland closely resembles that associated with primary Graves' disease in the human subject, and most of the symptoms of this disease are reproduced in the experimental animal by injection of the hormone. Loss of weight, tachycardia, nervousness, increased metabolic rate, and raised blood-iodine all occur, and even exophthalmos has been produced in the animal by some workers. With the exception of the exophthalmos, these effects are all due to a direct action of the hormone on the thyroid gland. They do not occur in the absence of the thyroid. That the hormone acts directly on the thyroid is shown by the fact that it produces the characteristic histological changes in slices of the gland surviving *in vitro*

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(Eitel, Krebs, and Loeser, 1933). Since removal of the anterior pituitary in animals results in a reversion of the thyroid to a resting inactive state, it may safely be concluded that in the normal animal the secretory tone of the thyroid gland is maintained by a continual stimulation from the pituitary through the mediation of this hormone. Although the effects of the thyrotropic hormone on the organism as a whole are apparently identical with those of the thyroid hormone, yet the two are entirely different substances and must not be confused. There are two fundamental points of difference. Firstly, the thyrotropic hormone is inactive in the thyroidectomized animal whereas thyroid hormone is still active. Secondly, the thyrotropic hormone stimulates to greater activity the normal thyroid gland whilst the thyroid hormone itself has the reverse effect.

Injection of the thyrotropic hormone produces in the experimental animal such a close imitation of human Graves' disease that it was clearly of the greatest interest to determine what rôle, if any, this hormone plays in the aetiology of Graves' disease and other thyroid disorders in man. A number of attempts have been made to do this, but although the hypothesis that Graves' disease is due to an over-production of thyrotropic hormone by the pituitary is a tantalizingly attractive one, yet conclusive evidence supporting such a hypothesis has remained persistently lacking. The results of workers on this problem have been surprisingly conflicting, and in this respect are in marked contrast to results obtained with the thyrotropic hormone itself. No doubt now exists that this hormone, as extracted from the anterior pituitary, stimulates the thyroid gland. In our own experiments it has never failed to do so to an unequivocal degree. Yet the very presence or absence of the hormone in blood or urine is still under dispute. The hopes of a greater insight into the pathology of thyroid disorders, which the discovery of this hormone aroused, have not as yet been fulfilled. Clinical and pathological experience indicates strongly that the hormone has some special function in the human subject and probably exists in the circulating blood. Clinical evidence pointing in this direction was collected by Cushing and Davidoff in 1927, before even the existence of the hormone had been definitely established. From a study of a large series of patients with acromegaly they concluded that the chromophile cells of the anterior lobe of the pituitary body secrete a substance which is capable of raising the basal metabolic rate. They left open the question of whether the action was a direct one on the tissue metabolism or whether it was achieved through the activity of the thyroid. Indications of hyperthyroidism are frequently found in association with acromegaly. In a series of 72 cases of acromegaly with chromophile adenoma, Cushing and Davidoff found the basal metabolic rate above +10 per cent. in 32 cases, the average figure of these being +26 per cent. Many of the cases in this series had enlarged thyroid glands and other evidences of hyperthyroidism. Operative removal of the pituitary tumour tissue resulted in an average drop in metabolic rate of 17 per cent. in a series of 17 cases. In hypopituitarism due to chromophobe adenoma,

on the other hand, 71 of a series of 107 cases had a basal metabolic rate below -10 per cent., and this low metabolic rate was not appreciably affected by operative removal of the tumour. The most extreme cases of hypopituitarism are to be found in the syndrome known as Simmonds' disease. In this condition the anterior lobe is found to be either atrophic or destroyed by inflammatory or carcinomatous involvement. The basal metabolism is always low, often extremely so, and the disease is usually associated with an atrophy of the thyroid gland. Graubner (1925) for instance, reviewing the reports of 33 cases of Simmonds' disease, found thyroid atrophy recorded in every case in which the condition of the gland was described. These changes in the thyroid gland and in metabolism are similar to those produced in the experimental animal by hypophysectomy. In such animals they can be entirely prevented by daily injections of the thyrotropic hormone. The same is also probably true for the human subject suffering from hypopituitarism with associated low basal metabolic rate. Lederer (1935), for instance, has shown in two such cases a well marked rise in the basal metabolic rate towards normal levels in response to thyrotropic hormone injections. Clinical indications such as these, considered in the light of the large amount of evidence now obtained from animal experiments, justify the conclusion that the thyrotropic hormone is in man, as in animals, the factor whereby the pituitary exerts its tonic control over the secretory activity of the thyroid gland. If this be so, then the hormone must presumably be present in the blood-stream. That this has not as yet been conclusively shown, is probably due to the great technical difficulties encountered in detecting the hormone in high dilution in body fluids.

In the present paper are recorded and discussed the results of experiments in which we have attempted to overcome these difficulties, with a view particularly to determining whether any evidence can be obtained of increased production of this hormone in the subjects of Graves' disease.

*Source of the thyrotropic hormone.* The thyrotropic hormone used in this work has, unless otherwise stated, been obtained by the method of Rowlands and Parkes (1934) from 'Undegreased anterior pituitary gland powder' kindly supplied by Messrs. Armour. This powder is extracted at room temperature with several volumes at 50 per cent. aqueous pyridine. The extract, centrifuged free from solid residue, is poured into a mixture of four volumes of alcohol and one volume of ether. A precipitate forms which is separated, washed with absolute alcohol and dried. This preparation is strongly thyrotropic, and, kept in a desiccator, has maintained its activity apparently undiminished for over eighteen months. The powder dissolves slowly but completely in N/20 soda, and this solution after neutralization is ready for subcutaneous injection. A dose of 5 mg., injected daily for five days after the technique of Parkes, doubled the mean thyroid weight in a series of five 180 gm. guinea-pigs, and so contained one Parkes unit of hormone. It is this relatively impure, but very active, extract which we refer to subsequently as the 'thyrotropic hormone' used in the experimental work.

*The detection of the thyrotropic hormone.* A survey of the existing literature dealing with the search for thyrotropic hormone in the human subject leads one to the conclusion that the main cause for the very conflicting results of various workers is a difference in the interpretation of the criteria by which the presence or absence of the hormone is judged. For this reason it is desirable to deal at some length with our own criteria. The most convenient test object for the hormone is the young guinea-pig of from 160 to 200 gm. body-weight, and this has been used throughout the present work. The substance to be tested is injected in four or five daily doses subcutaneously into the guinea-pig, which is then killed by chloroform on the day following the last injection. The thyroid glands of both sides are carefully dissected out, freed from adherent moisture, and weighed before being fixed in 10 per cent. formol saline. Sections of both lobes are then cut in the longitudinal axis and stained with haematoxylin and eosin. The presence of thyrotropic hormone in the injected fluid is shown by histological evidence of activity in these thyroid glands.

When the injected fluid contains large amounts of the hormone, three criteria may be used in detecting the resultant activity of the guinea-pig thyroid. Firstly, the actively stimulated gland betrays itself during dissection by its increased size, greater vascularity and greater firmness. Secondly, the weight is increased, and the weight change has been employed by Rowlands and Parkes (1934) in the quantitative assay of the hormone. Thirdly, there is the histological picture. The actively stimulated gland shows, in its advanced form, a complete absence of colloid from the vesicles. The epithelium of practically all the vesicles is higher than normal, and usually presents a rather swollen aspect. At its lowest it is cubical, at its most typical, a low columnar epithelium. By enlarging centripetally it makes the lumen of the vesicles smaller. The cell nuclei are large, spherical, and appear swollen. Increased vascularity is frequently evident in the stained sections. In contrast to this picture, the resting thyroid of the young guinea-pig has larger vesicles, full of a firm colloid staining well and uniformly with eosin. The epithelium of the majority of the vesicles is flat, sometimes extremely so. The nuclei are elongated with their long axes parallel to the basement membrane. Towards the centre of the gland this resting appearance is often less marked. The epithelium tends to be cubical, the nuclei are rounder, the colloid stains less well with eosin and may show evidence of partial absorption. This apparent slight activity, which is frequently found in the normal young guinea-pig thyroid, is of considerable importance, for it may be readily mistaken for evidence of a slight stimulant action of the injected test substance. Attention has been called to it by several workers, notably del Castillo (1932) and most recently McGinty and McCullough (1936). Ignorance of its occurrence may lead to the apparent detection of the hormone in substances in which it is not in fact present. Knowledge that it may occur makes the detection of small quantities of the hormone extremely difficult. It has been our impression that under the influence of the thyrotropic hormone this

central activity is increased and spreads towards the periphery until finally it involves the whole gland, and this also appears to have been the opinion of Aron (1930). If, in the thyroid of an injected guinea-pig, the vesicles in the periphery of the gland show evidence of hyperplasia and colloid absorption, there need be no reasonable doubt that the gland has been stimulated beyond its normal limits, and hence that the injected material contained a thyrotropic substance. But when this normal central hyperplasia has not extended to involve the peripheral vesicles, much difficulty is experienced in deciding whether or not the gland has been stimulated beyond normal limits. Because of the element of doubt in such glands, we have not regarded them as showing definite stimulation. Positive results have been claimed only when the hyperplasia has extended to involve some or all of the vesicles in the periphery of the gland. The manner of fixation of the thyroid tissue preparatory to sectioning has a considerable influence on the histological appearance. We have used formol-saline throughout as fixative in preference to Bouin's solution, because the former has appeared to show up more clearly the differences between the resting and hyperplastic epithelium. Resting thyroid tissue fixed in Bouin's solution shows an epithelium which is higher than that of the same gland fixed in formol-saline. And this higher epithelium more nearly approaches in appearance that of the hyperplastic epithelium.

In the light of the preceding considerations of normal thyroid histology in the guinea-pig, we have distinguished four chief types of histological picture :

1. The first group comprises those glands which by all the histological criteria are inactive. The greater part of the section shows intact well-stained colloid in vesicles lined by flat epithelium. The presence of a small area in the centre of the gland showing cubical epithelium and some evidence of colloid resorption was regarded as normal and did not suffice to bring the gland into the second group.

2. The second group includes those glands in which the central area of moderate activity was larger and extended from half to two-thirds of the way to the periphery. In this group colloid was intact in practically all the more peripheral vesicles, and the epithelium of these was either flat or low cubical. These glands were not regarded as showing evidence of definite stimulation. It is apparently over the interpretation of glands of this type that conflict arises between different workers. There can be little doubt that a very slight stimulation of thyroid gland by thyrotropic hormone will produce a histological picture falling in this group. But we have not felt ourselves able, in this work, to distinguish with certainty such slight degrees of thyroid stimulation over the normal.

3. The third group is that regarded as showing definite moderate stimulation of the gland. In such glands signs of greater or less resorption of colloid extend right to the periphery, and many of the peripheral vesicles have a definitely cubical epithelium. There is also included in this group a type of gland to which attention has been called by Guyénot, Ponse, and Dottrens (1935) and which we have occasionally encountered. In this the epithelium is fully hyperplastic right to the periphery but colloid absorption is relatively slight. The appearance is well illustrated in Fig. 59 on page 125 of their paper and is called by these authors the '*réaction épithéliale précoce*'.

4. The fourth and final group in our histological classification includes all those glands in which cubical or low columnar epithelium is found in all vesicles right to the periphery, and in which only occasional scattered vesicles are found containing persisting colloid. These glands are fully hyperplastic.

In detecting colloid absorption in the intermediate stages we have not felt justified in taking the presence of vacuoles as evidence. Absorption is with much greater certainty revealed by a diminution in the staining power of the colloid for eosin, and in the appearance of a fine poorly-stained fibrillary network in place of the uniformly stained structureless colloid of the resting vesicle. Although Severinghaus (1933) considers these vacuoles to be primarily phenomena of colloid absorption, yet this view does not appear to be universally accepted. Throughout we have laid much more stress on the histological picture than on the thyroid weight. But since Rowlands and Parkes (1934) have proposed increase of thyroid weight as a method of assaying the thyrotropic hormone, it is of interest to determine to what extent our histological grouping is reflected in increase of thyroid weight.

In Fig. 1 is plotted the weight distribution of glands in each of the four histological groups. To eliminate as far as possible the effects of varying body-weight, the thyroid weight has been expressed in mgm. per 100 gm. of guinea-pig body-weight. As the range of body-weights is relatively small, this affords an adequate correction. It will be seen that weight forms a fairly reliable method of distinguishing between groups I and IV, though occasional exceptions do occur. Large glands are not infrequently found which are quiescent, and more rarely a fully hyperplastic gland is encountered, the weight of which remains within normal limits. But the degree of weight scattering in groups II and III is so large, and the overlap so great, that thyroid weight alone is clearly of no value as a criterion of slight secretory activity. It is only of value when the quantities of hormone used are considerable, much higher in fact than are likely to occur in biological fluids other than extracts of the pituitary gland itself. It is probable that many of the discrepancies, which have been encountered between histological picture and thyroid weight, are due to the fact that the test fluids injected contained other contaminating substances influencing thyroid weight. Evidence suggestive of this has been obtained with some of our urine extracts. But even if this be so, it merely serves to stress the unreliability of thyroid weight alone, as an indicator of thyrotropic activity in fluids which may contain other complicating factors.

#### *Experimental*

*Thyrotropic hormone in the human pituitary.* That the human pituitary contains thyrotropic hormone in its anterior lobe has already been demonstrated by Muller, Eitel, and Loeser (1935). We have been able readily to confirm this fact. Six human pituitaries were obtained from routine post-mortem examinations on young adult subjects. The anterior lobes were

desiccated in a large volume of acetone and then dried in a desiccator over sulphuric acid. The dried glands were shredded, ground in a mortar, and extracted with 50 per cent. aqueous pyridine according to the technique already described for the preparation of an active extract from beef pituitaries. The precipitate produced on pouring the pyridine extract into the ether-alcohol mixture weighed when dry 150 mg. Fifteen mg. of this powder

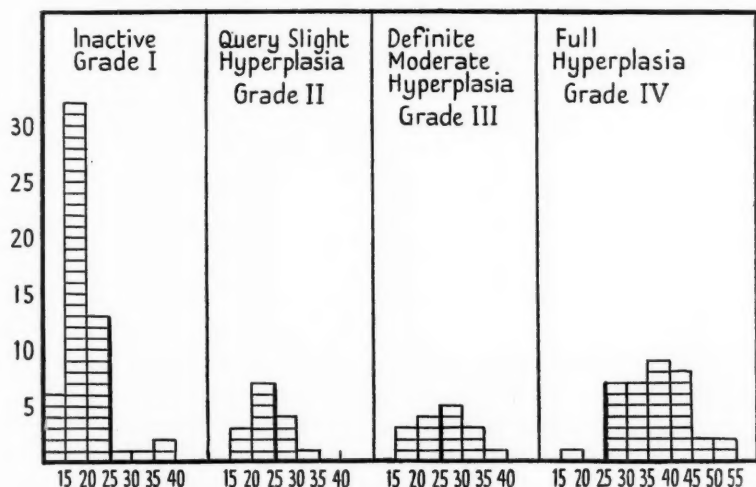


FIG. 1.

was dissolved in N/20 soda, neutralized and injected daily for five days into each of two young guinea-pigs of about 170 gm. body-weight. The animals were killed on the sixth day and their thyroids found to weigh respectively 40 mg. and 48.6 mg. Both glands on section showed well marked and unequivocal evidence of hyperplasia, the former of grade III and the latter grade IV.

*The thyroidectomized rabbit.* Publication of the work dealt with in this paper was delayed for a considerable time, because much of it was negative in result, and it was felt that the significance of a series of negative findings would be small, unless some contrasting condition was found in which positive evidence of thyrotropic activity could be shown in the blood. It was highly desirable to do this in order to justify the methods and criteria of activity which we have used. The thyroidectomized rabbit finally provided the desired condition. Four rabbits were originally used which had been thyroidectomized four months previously. They were bled from the ear vein, and serum so obtained was injected in 2 c.c. doses daily for five days into test guinea-pigs. Two of these sera showed no evidence of thyrotropic activity, but in the remaining two it was quite unequivocal, and was, moreover, still present in each case in serum obtained by a second bleeding a fortnight later. In a second series of four thyroidectomized rabbits, thyrotropic activity was again detected definitely in the serum of two. We are not concerned in the

present paper with the reasons for the failure of the hormone to appear in some of the thyroidectomized animals. It is possible that this is due to the presence of residual fragments of thyroid tissue, and this possibility is at present under investigation. It is the fact that thyrotropic activity does, indeed, appear in the blood of a certain proportion of these rabbits, which is of importance in the present paper. For such positive results show that

TABLE I  
*Serum of Thyroidectomized Rabbits.*

Guinea-pig No.	Donor Rabbit. No.	Thyroid.		Histology grade.
		Weight. mg.	per 100 g.-pig.	
229	2	72.0	29.0	IV
234	2	57.5	34.4	IV
230	3	44.0	26.7	IV
236	3	48.0	27.2	III
228	4	47.0	21.2	I
235	4	32.5	20.2	II
245	5	37.0	19.0	I
246	5	32.5	19.2	I

under favourable circumstances the concentration of thyrotropic hormone can rise sufficiently high in the animal body for it to become detectable by the relatively strict criteria employed in this investigation. They thus provide a valuable control experiment, and enhance considerably the significance of the negative results obtained with the sera of human Graves' disease.

*Thyrotropic hormone in human blood.* If thyrotropic hormone is present in normal blood, as indirect clinical and physiological evidence leads us to suppose, then its concentration is so low that it cannot with certainty be detected in the relatively small quantities of serum which can be injected into a test animal. Two c.c. doses of various normal human and rabbit sera have been injected daily into guinea-pigs for five days, and in no case has the degree of hyperplasia found subsequently in the thyroid glands of these animals exceeded that slight degree liable to occur in the untreated animal. If the hormone is to be detected with certainty in normal blood then it would seem that means of concentrating it must be found. So far as we are aware, the only method which has been suggested for so doing is that of Fellingner (1936). In this the blood is laked, and the main bulk of the proteins is precipitated with 40 per cent. acetone. This precipitate is filtered off, and the concentration of acetone in the filtrate is raised to 85 per cent. A second precipitate is thereby obtained which is washed with acetone and dried. The resultant brownish powder is extracted with slightly acidified water at room temperature, and this extract, after neutralization, is ready for injection into the guinea-pig. Using this method of concentration, Fellingner claims to have been able to demonstrate the presence of thyrotropic hormone in quantities of human blood as small as 10 c.c. We have been able easily to satisfy ourselves that when thyrotropic hormone is

added to either human or sheep blood, much of it can be recovered by Fellingner's process. Fifty mg. of our active 'thyrotropic hormone' was dissolved in weak alkali and added to 100 c.c. of sheep's blood. The final extract of this blood obtained by Fellingner's method had a volume of 10 c.c. Of this extract 2 c.c. was injected daily into a guinea-pig for five days. Two guinea-pigs so treated were killed on the sixth day, and the thyroid

TABLE II  
*Fellinger Extracts of Blood.*

Guinea-pig No.	Blood.		Added hormone. mg.	Thyroid.		Histology grade.
	Source.	Volume. c.c.		Weight. mg.	per 100 g.-pig.	
237	Sheep	50	—	43.0	23.2	I
217	"	100	50	35.0	15.9	IV
238	"	100	—	39.5	17.7	I
215	"	100	50	50.0	30.0	III
214	"	250	—	52.0	26.1	I
216	Rabbit	50	—	31.5	15.7	I
239	Human	75	—	37.0	15.5	I
240	"	75	—	38.1	15.9	I
232	"	60	—	25.5	15.7	I
219	"	100	—	46.2	19.9	I
241	"	100	25	61.0	25.9	IV
242	"	100	25	73.0	32.0	IV
243	(Serum)	60	—	33.5	16.7	I

glands of both showed full or grade IV hyperplasia with practically complete disappearance of colloid. Two other guinea-pigs were each similarly treated with extracts of 100 c.c. samples of human blood, to which 25 mg. of 'thyrotropic hormone' had been previously added. The thyroid glands of both were much increased in weight and showed full grade IV hyperplasia. But extracts of normal blood of the rabbit, sheep, and human being obtained by the same procedure have completely failed to show any evidence of thyrotropic activity. Indeed, volumes of human blood and sheep blood, five or more times as large as those found active by Fellingner, have provided extracts which showed no more than a slight and highly equivocal degree of activity.

*Graves' disease.* Blood-serum from human cases of well marked primary thyrotoxicosis has been injected into test guinea-pigs in doses of 2 c.c. daily for five or six days. In none of the nine guinea-pigs so treated was there the slightest evidence of thyroid stimulation. Indeed, the impression was gained that the thyroids of such animals were more inactive than the normal. The glands appeared smaller, and the epithelium of the vesicles seemed more consistently flat. This apparent tendency is to some extent borne out by the weights of the thyroids, which average 16 mg. per 100 gm. body-weight, as compared with an average of 17.6 mg. in a normal untreated series. The depressant effect of the serum of Graves' disease on the activity of the thyroid gland has been revealed more clearly in another way. A series of five young guinea-pigs was injected daily for six days with 2 c.c. of Graves'

disease serum taken from five different patients, none of whom were under treatment with Lugol's iodine. On the third to sixth days 5 mg. of 'thyrotropic hormone' was also injected into each animal. All were killed on the seventh day. The mean thyroid weight of these animals was 25.9 mg. per 100 gm. body-weight. A control series of five guinea-pigs was treated in precisely the same manner, with the sole difference that normal human serum was substituted for the Graves' disease serum. In this series the mean thyroid weight was 33.6 mg. per 100 gm. body-weight. Thus Graves' disease serum, far from containing a thyroid stimulating factor, actually has a partial inhibiting effect on the stimulant action of the thyrotropic hormone. There are two possible causes for such an effect. One is the presence in the serum of an antithyrotropic factor of the type first described by Collip (1934 *a*). This factor has a specific effect in inhibiting the action of the thyrotropic hormone. The other possibility is that the effect is due to the excess of thyroid hormone in the blood, for this hormone is well recognized to depress the activity of the thyroid gland itself. Distinction can be made between these two possibilities by measurement of the metabolic rate of the injected animals. If the effect be due to an antithyrotropic factor of the Collip type, then the metabolic rate should be lower than in the controls, for Collip has shown that in the presence of the antithyrotropic factor, the thyrotropic hormone is unable to produce such a large rise in metabolic rate. If, on the other hand, the effect be due to thyroid hormone itself, then the metabolic rate should be higher than in the controls, for it is reasonable to assume that the stimulant effect of thyroid on metabolism will be added to that of the thyrotropic hormone. Experiments have therefore been undertaken in an attempt to elucidate this point. Metabolic rate determinations in young guinea-pigs were made with the apparatus described by Richards and Collison (1928). This apparatus, slightly modified in detail, was found to give reliable results and to be very convenient in use. It was not found possible, however, to obtain sufficiently constant metabolic rates in untreated animals for the effects which were sought to be clearly demonstrable. Day to day variations in metabolic rate proved to be too large for any small stimulant or depressant of the Graves' disease serum to be revealed. Better and more significant results were, however, obtained if thyrotropic hormone was given together with the serum under test. In Fig. 2 are shown the mean results obtained on a series of animals tested in this way. Curve A shows the rise in metabolic rate produced by 5 mg. daily of our 'thyrotropic hormone'. The double rise to which attention has been called by Collip (1934 *b*) is well seen in this curve, which is the average of those obtained on four animals. If normal serum is injected together with the hormone, the rise in metabolic rate is less, and the double peak is smoothed out. This is shown in curve B. Normal human serum thus has an inhibiting effect on the action of the thyrotropic hormone. In curve C is shown the result of substituting Graves' disease serum for that from normal persons. The rise in metabolic rate has been inhibited, but not so markedly as with normal serum. Thus the serum

of Graves' disease has relatively a more stimulant action on metabolism than has normal serum. If Graves' disease serum had contained an antithyrotropic factor of the Collip type, the reverse effect would have been expected. But both the effect on the metabolic rate and the action on thyroid gland weight and histology are in accord with the view that the active agent concerned is the excessive quantity of thyroid hormone present in the circulating blood in Graves' disease.

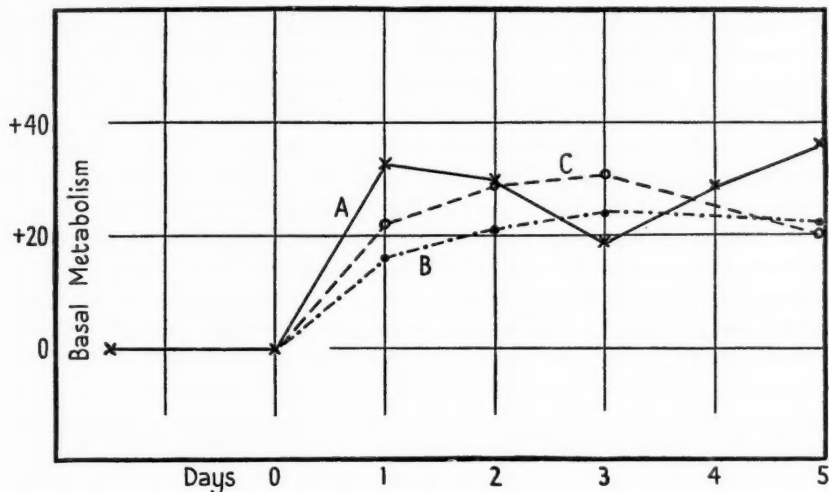


FIG. 2.

Attention has already been called to the antithyrotropic action of excessive amounts of thyroid hormone by Fellingner (1936), who considers it to be responsible for the failures of earlier investigators to detect thyrotropic hormone in the serum of Graves' disease. But even if this be true, it does not alter the fact that the balance of hormones in the serum of Graves' disease is such as to result in an inhibiting effect on the thyroid gland rather than a stimulating one. Even if thyrotropic hormone is present in Graves' disease serum, as Fellingner claims, its action on the thyroid gland of the guinea-pig is apparently counteracted by that of the circulating thyroid hormone. It is difficult, therefore, to ascribe the excessive stimulation of the thyroid gland of the Graves' disease subject to this cause.

*Myxoedema.* We have had the opportunity of examining only three samples of serum from two cases of well-advanced and untreated spontaneous myxoedema. Both cases were typical examples of the disease, the basal metabolic rate in one being - 45 per cent. and in the other - 30 per cent. In none of these samples was there any trace of thyrotropic activity. In this failure to find evidence of increased thyrotropic hormone production in myxoedema, our results are in agreement with the experience of Spence (1937), who also failed to find the hormone in the serum of similar patients. But such negative

findings do not, at first sight, agree with the claims of Hertz and Oastler (1936) that the hormone is increased in the serum of patients suffering from myxoedema which has resulted from complete thyroidectomy. Possible reasons for this discrepancy will be considered later in this paper.

*Thyrotropic hormone in the urine.* By analogy with the sex hormones which, it is now well known, are excreted in greater or less amount in the urine, it was possible that the thyrotropic hormone might also be detectable in that fluid. Indeed, such a possibility has already attracted the attention of a number of workers, but as yet no unanimity of results has been attained. As long ago as 1930 it was claimed by Aron and Klein (1930, 1932) that normal urine contains a small but detectable amount of thyrotropic hormone, and that this was much reduced in the urine of Graves' disease. Aron injected fresh untreated urine into his test guinea-pigs, and found discrete hyperactive areas, usually limited to the centre of the gland and always of slight but similar degree. Krogh and Okkels (1933 *a, b*) tried to confirm these findings of Aron, but although they concentrated much larger volumes of urine, they were unable definitely to establish the presence of the hormone in either normal or Graves' disease urine. In 1934 Giedosz, using rabbits as test objects, injected human urine intravenously and obtained scattered changes in the thyroids of 50 per cent. of his animals. These changes he attributed to the presence of thyrotropic hormone in the urine. Hellwig (1933), also using as material rabbits which had been injected with female urine for pregnancy tests, found evidence of thyroid hyperplasia in 70 per cent. The rabbit, however, is an unsuitable animal for such experiments, as the histology of its thyroid gland is very inconstant. Also, Guyénot, Ponse, and Dottrens (1935), who used guinea-pigs as test objects, have denied that human pregnancy urine is thyrotropic, but Houssay (1932) claims to have confirmed the finding of Aron, that the urine of rats is rich in thyrotropic activity. In 1933, Smith and Moore failed to find the thyrotropic hormone in the urine of Graves' disease subjects, nor could they detect it in the urine of guinea-pigs which had been injected previously with large doses of the hormone. Still more recently Antognetti and Geriola (1936) have tried unsuccessfully to confirm the claims of Aron. They could obtain no evidence of thyrotropic activity in extracts of the urine of normal persons, or of patients suffering from Graves' disease or myxoedema.

Thus it is seen that opinion is by no means unanimous on the presence of thyrotropic hormone in normal urine, though most observers agree that there are only very small traces in the urine of Graves' disease. Since the hormone appears to be relatively stable in solution at room temperature, it seems unlikely that the discrepancies are due to differences of technique of the various investigators. It is far more probable that they are due to differing interpretations of the histological picture seen in the thyroid glands of the test guinea-pigs. In this regard the central area of hyperplasia which frequently occurs in the thyroids of untreated animals, and to which

attention has already been drawn, is a source of difficulty and possible error. Uncertainty from this cause can be successfully overcome only by increasing the quantity of hormone injected into the animal. If the hormone is present at all in such urines, it is clearly only in very low concentrations, and sufficiently large quantities of such urines cannot be injected into young guinea-pigs to produce unequivocal results. It is highly desirable, therefore, that methods should be found whereby any thyrotropic hormone present can be concentrated from large volumes of urine, and taken up into a solution of much smaller bulk for injection. We have devoted considerable time to the search for suitable methods of concentration because it was felt that conclusive results were more likely to be obtained in this way, than by attempting a finer and finer discrimination of slight histological changes in the thyroid glands of animals treated with very small quantities of thyrotropic hormone. If the thyrotropic hormone is actually present in normal human urines, as Aron and his co-workers claim, then it should be possible by suitable methods of concentration to obtain sufficient quantities of the hormone from such urines, to stimulate a guinea-pig thyroid into an unequivocal degree of activity. The majority of the workers quoted above have not employed such concentration methods, but have based their conclusions on experiments in which only two or three c.c. of urine were injected daily. But Krogh and Okkels (1933) used alcohol precipitation to concentrate large volumes of urine, and more recently Antognetti and Geriola (1936) used a somewhat similar method. Both groups of workers obtained negative results in the urine of Graves' disease.

In our own attempts to find the thyrotropic hormone in urine, we have made use of two separate methods, both of which we have been able to satisfy ourselves do greatly concentrate the hormone when it has been added previously in low concentration to the urine samples.

*Methods of concentrating thyrotropic hormone from urine.* (a) Alcohol-ether precipitation. It was clearly shown by the work of Rowlands and Parkes (1934) that the hormone is completely precipitated by adding to the solution containing it a mixture of four volumes of alcohol and one volume of ether. We have been able easily to confirm this fact, and have made use of it as a concentration method on large volumes of urine. The urine is made neutral to litmus and is then poured into four volumes of alcohol and one volume of ether. A white precipitate forms at once which is probably largely phosphates. The mixture is allowed to stand overnight in a cool room and the precipitate is then removed by centrifuging, washed with alcohol and dried in a desiccator. The greater part of the resultant powder is insoluble in weak alkali. To prepare the extract for injection it is treated with N/20 alkali, the insoluble residue is centrifuged down and the supernatant fluid neutralized with weak acid. Alternatively the whole precipitate may be injected as an aqueous suspension. By this method it has been possible satisfactorily to recover 25 mg. of the 'thyrotropic hormone' when dissolved in 100 c.c. of urine. The method has several disadvantages. A large volume of alcohol is required if much urine is to be treated, and the resulting dried extract is bulky and largely insoluble. Furthermore, the yield appears to be

relatively low and probably does not exceed 50 per cent. In the second method of concentration all these disadvantages have been eliminated.

(b) Benzoic acid precipitation. It was shown by Greep (1935) that the thyrotropic hormone is carried down in the bulky precipitate formed when sodium benzoate is acidified to benzoic acid. This property has been found eminently suitable for the recovery of thyrotropic hormone when it has been added in small amounts to either human urine or rabbit's urine. For reasons which we have not investigated, the procedure does not seem to be so successful in recovering the hormone from weak aqueous solutions. The urine, if acid, is made slightly alkaline to litmus by the addition of soda. Any precipitate of phosphates is not removed. Sodium benzoate previously dissolved in a small quantity of water is then added in the proportion of 20 gm. of benzoate to each litre of urine. The whole is well mixed and hydrochloric acid is added gradually with frequent shaking. At first any precipitate of phosphate is redissolved and then, as more acid is added a heavy precipitate of benzoic acid appears. Acid is added until complete precipitation of all the benzoic acid has taken place. This has been achieved when the solution becomes slightly acid to Congo red. The mixture is well shaken and the precipitate filtered off on a Buchner funnel. It is washed with slightly acidified water and then sucked as dry as possible. The yellowish-white precipitate is removed from the funnel and dissolved in excess of acetone in a wide-mouthed flask. For each 20 gm. of sodium benzoate originally used, 400 c.c. of acetone will usually be sufficient. The benzoic acid dissolves readily but leaves a small flocculent residue which contains the active substance. The whole is left to stand overnight in a cold room. It is necessary to suck the precipitate as dry as possible before solution in the acetone because the concentration of water in this solution must be kept as low as possible. The thyrotropic hormone remains insoluble only when the concentration of water is low. Hence, if the precipitate is moist, further acetone may have to be added to increase its concentration. The residual flocculent precipitate is centrifuged down, washed with acetone to free it from benzoic acid, and dried in a desiccator. The yield is variable but is usually 100 to 200 mg. of grey powder from each litre of urine. The dry powder is almost completely soluble in N/20 sodium hydroxide and such a solution after neutralization is ready for injection. By means of this method it has been possible to recover almost completely 50 mg. of the 'thyrotropic hormone' which had been dissolved in 100 c.c. of urine.

For convenience, extracts prepared by means of these two methods will be referred to as alcohol-ether and benzoic acid concentrates respectively, and in the tables still more briefly as A.E. and B.A.

The thyroid glands of guinea-pigs treated with alcohol-ether, and benzoic acid concentrates of normal urine are, as a rule, considerably larger than those of untreated animals. But this enlargement is not associated with any evidence of stimulation. The mean thyroid weight of a series of untreated guinea-pigs was 17.6 mg. per 100 gm. of body-weight, whereas in four animals injected with extracts of normal urine it averaged 27.0 mg. Two of these guinea-pigs had received benzoic acid concentrates of 2.5 litres of urine each, this being a mixed sample obtained from a number of healthy young medical students. In neither was there any sign of hyperplastic stimulation, in spite of the increase in size. This increase in size is also produced by

concentrates of Graves' disease urine obtained by either process. The mean thyroid weight of a series of eleven animals so treated was 25.5 mg. per 100 gm. of guinea-pig as compared with the normal of 17.6 mg. In contrast to this it has not been produced by similar extracts of urine from Graves' disease patients under treatment with Lugol's iodine. A series of urines from six such cases gave a mean thyroid weight of only 19.6 mg. per

TABLE III  
*Concentrates of Human Urine*

Guinea-pig No.	Urine vol. c.c.	Added hormone mg.	Conc. method	Thyroid		Histology grade
				Weight mg.	per 100 g.-pig	
55	100	—	A.E.	45.6	25.4	I
56	100	—	A.E.	43.0	24.1	I
212	2,500	—	B.A.	41.0	28.2	I
213	2,500	—	B.A.	53.0	30.5	I-II
6	100	75	A.E.	50.0	25.8	IV
8	50	25	A.E.	47.0	31.3	IV
193	40	50	B.A.	86.0	35.4	IV
184	100	50	B.A.	78.0	35.0	IV
185	100	25	B.A.	56.5	27.7	IV

TABLE IV  
*Concentrates of Graves' Disease Urine*

Urine vol. c.c.	Conc. method	Lugol's iodine	Thyroid		Histology grade
			Weight mg.	per 100 g.-pig	
120	A.E.	No	48.0	21.8	I
120	A.E.	No	32.5	20.0	I
120	A.E.	No	63.0	37.0	II
100	A.E.	No	29.4	15.0	I
100	A.E.	No	34.0	18.9	I
100	A.E.	No	62.0	35.4	III
120	A.E.	Yes	25.0	14.2	I
120	A.E.	Yes	56.5	30.9	II
100	A.E.	Yes	40.0	19.0	II
100	A.E.	Yes	27.4	17.8	I
100	A.E.	Yes	30.9	16.8	I
500	B.A.	No	71.0	30.6	II-III
1,200	B.A.	No	61.0	28.0	III
1,000	B.A.	No	55.0	24.4	II
1,000	B.A.	Yes	36.0	18.0	I
2,000	B.A.	No	36.0	21.0	I
1,000	E.A.	No	39.0	26.5	I

100 gm. of body-weight. Nor is it produced by concentrates of the urine of spontaneous myxoedema. In eight guinea-pigs treated with myxoedema urine concentrates in large amount, the mean thyroid weight was only 18.5 mg. per 100 gm. body-weight, a figure not significantly above the normal.

It is of interest that Aron and Klein (1930, 1932) noted a similar increase in weight of the thyroid glands after the injection of 3 c.c. of human urine

daily for five days, and although our concentrates correspond to a far larger quantity of urine, the weight increase is of practically the same degree as was observed by them. These weight changes are, in our opinion, quite independent of hyperplasia, and therefore we feel they cannot be due to the presence of the thyrotropic hormone. They may, however, be due to one of the other hormones known to occur in urine. They are of importance in that they show clearly that in such investigations weight alone is a quite unreliable index of thyrotropic activity. These glands resemble more closely a colloid goitre than a thyrotoxic one. Using the histological criterion, we have been quite unable to detect thyrotropic activity in normal urine by either concentration process. When thyrotropic hormone is added in low concentration to urine, it is recovered readily by the benzoic acid technique, the yield being apparently a very high one. Yet the benzoic acid concentrate of 2.5 litres of mixed normal urine from a number of young adults was entirely without thyrotropic activity when injected into a guinea-pig. We are driven to the conclusion, therefore, that normal urine does not contain this hormone in significant amounts. There appears to be only one possibility which would render this conclusion false, namely, that the hormone exists in urine in a form having quite different physical properties from those of the active substance extracted from the pituitary, and has properties which prevent its being concentrated by either of the methods which have been employed successfully for the latter substance. In the urine of Graves' disease similar results are obtained and similar conclusions must be drawn. In a series of urines from 17 cases of Graves' disease definite thyrotropic activity was observed only twice. A third case was suggestive and the remainder were entirely negative. It is possible, therefore, that there is a type of Graves' disease associated with increased thyrotropic hormone production. It is of interest in this regard, that Krogh and Okkels (1933*a*) found definite evidence of thyrotropic activity in the urine of one of the nine cases of exophthalmic goitre which they examined. We have been unable to detect any points of clinical difference whereby these cases could be distinguished from the rest, and they appear to form a minority of those classed as primary Graves' disease. In the urine of two cases of spontaneous myxoedema we have also failed completely to find any trace of thyrotropic activity. Concentrates of volumes of urine up to two litres injected into a series of eight guinea-pigs did not alter in any way the histological picture. Such negative results contrast with the work of Hertz and Oastler (1936), who found that the urine of patients with myxoedema, following complete therapeutic thyroidectomy, possessed thyrotropic activity, but it is felt that from the endocrine standpoint the two types of myxoedema are not necessarily comparable, except in so far as absence of thyroid tissue is common to both. Furthermore, in contrast to our own negative results on myxoedema urine and serum, we have been able to satisfy ourselves that in rabbits, after thyroidectomy, the titre of thyrotropic hormone in the serum is often demonstrably raised. Such animals are much more comparable to the type

of case studied by Hertz and Oastler. These positive results in the rabbit are of great value in that they increase considerably the significance of the negative findings in human spontaneous myxoedema and in Graves' disease.

TABLE V  
*Concentrates of Myxoedema Urine*

Urine vol. c.c.	Conc. method	Thyroid		Histology grade
		Weight mg.	per 100 g.-pig	
500	A.E.	24.0	17.8	I
500	A.E.	24.3	18.0	I
400	B.A.	36.0	17.7	I
400	B.A.	40.0	20.6	I
700	B.A.	33.0	18.8	I
800	B.A.	35.5	17.4	I
2,000	B.A.	33.0	18.6	I
2,000	B.A.	33.5	19.9	I-II

#### *Discussion*

So many and varied are the recently discovered influences of the pituitary on other endocrine organs, that there is at the present time a great temptation to ascribe almost all endocrine functional disorders to the pituitary, but to do so without definite evidence is quite unjustifiable. The discovery of the physiological properties of the thyrotropic fraction of the pituitary hormone at once encouraged the hope that a greater insight into the aetiology of Graves' disease might soon be achieved. The hormone produces a stimulation of the thyroid gland which closely imitates Graves' disease. In both conditions the thyroid is overacting, and in both the nervous and metabolic effects of such overaction can be observed, but the similarity may go no deeper than this. Evidence positively implicating the thyrotropic hormone in the aetiology of Graves' disease is still lacking. Evidence has been presented in this paper which tends to show that the serum of the Graves' disease subject has usually an inhibiting rather than a stimulant effect on the thyroid gland of the young guinea-pig. It is not unreasonable to expect that the normal human thyroid would also be inhibited by such serum. Yet the patient's own thyroid in Graves' disease does not succumb to the inhibitory action of his or her own serum.

It is well known that thyroxin, and probably, also, the thyroid hormone itself, both act on the thyroid in a manner antagonistic to that of the thyrotropic hormone. We have already given reasons for believing that the antagonism observed between Graves' disease serum and the thyrotropic hormone is due to the high content of the former in thyroid hormone. It seems possible, therefore, that the hyperplastic tissue of the Graves' disease thyroid gland has in some way freed itself from the control which its own hormone would normally exert over it, a control tending to limit any overaction. If this should be so, then the pituitary must be regarded as innocent of any part in the aetiology. It is possible, indeed, that it is acting in

a manner calculated to restore the normal endocrine balance by secreting less than the normal amount of thyrotropic hormone. Evidence of such a restorative behaviour of the pituitary is found in the increase in thyrotropic hormone in the blood after thyroidectomy. Aron and his co-workers hold the view that there is less circulating thyrotropic hormone in the Graves' disease subject than in the normal, but although our own results are compatible with this view, we feel that we are scarcely able at the present time to eliminate the possibility that the whole of the difference between Graves' disease and normal serum in this respect is due to the antagonistic action of the excess thyroid hormone in the former.

The exophthalmos so characteristic of Graves' disease remains in either case unexplained. Many workers have been able to produce experimental exophthalmos in animals by injections of thyrotropic hormone, but there is no evidence that the thyrotropic hormone is increased in Graves' disease serum. Furthermore, Marine and Rosen (1934), and later Smelser (1936), have found that experimental exophthalmos is more readily produced after thyroidectomy in animals, whereas in man it is most typically associated with an overacting thyroid. Hertz and Oastler (1936) found definite evidence of increased circulating thyrotropic hormone in a series of cases of myxoedema resulting from thyroidectomy, and our own experiments support the view that increased circulating hormone is present in this condition. Such conditions are precisely those found by Marine and Rosen to be most favourable for the development of exophthalmos, and yet, so far as we are aware, no tendency to exophthalmos was observed in the cases of myxoedema studied by Hertz and Oastler, and none was noted in our own rabbits. In conditions of hypothyroidism, as in those of hyperthyroidism, the pituitary appears to behave in a manner calculated to restore a more normal endocrine balance. Stoppage of the supply of thyroid hormone to the blood-stream by thyroidectomy results in a compensatory increase in the output of thyrotropic hormone from the anterior pituitary lobe, but this extra hormone fails to achieve the desired restoration of thyroid activity, because the gland on which it should act has been removed. The failure of Spence (1937) and the present writer to demonstrate the existence of any similar compensatory increase of thyrotropic hormone in the serum of spontaneous myxoedema indicates that in this condition the pituitary has failed to respond to the diminishing supply of circulating hormone. It seems probable, therefore, that some cases of spontaneous myxoedema are caused by a primary failure of the thyrotropic hormone production of the pituitary, but as yet no definite evidence of this failure is available.

#### *Summary*

1. Clinical and experimental evidence indicates that the secretory activity of the thyroid gland is under the control of the anterior lobe of the pituitary gland through the mediation of a thyrotropic hormone.

2. This hormone has been shown to be present in the human pituitary gland.

3. The hormone is present in increased amount in the blood of rabbits which have been thyroidectomized.<sup>2</sup>

4. Normal human serum has not been found to possess any similar thyrotropic activity.

5. The serum of patients with Graves' disease has been found to have a depressant rather than a stimulant effect on the thyroid glands of guinea-pigs. Reasons are given for believing that this depressant action is due to the excessive amounts of thyroid hormone in the blood.

6. The serum from two cases of spontaneous myxoedema showed no trace of thyrotropic activity.

7. Two methods are described whereby the thyrotropic hormone may be concentrated when it is added experimentally in high dilution to urine.

8. Concentrates of large volumes of urine from both healthy and Graves' disease subjects have been prepared by these methods and have failed to show any trace of thyrotropic activity, except in two of the 17 cases of Graves' disease examined.

9. The concentrates of both normal and Graves' disease urines cause an increase in weight of the thyroid gland of the guinea-pig which is not associated with hyperplasia. This action is not shown by the urine of myxoedema, nor by the urine of Graves' disease subjects under treatment with Lugol's iodine.

10. The evidence collected does not suggest that the anterior pituitary gland is usually responsible for the hyperthyroidism of primary Graves' disease, but failure of thyrotropic hormone production may well be a causative factor in some cases of myxoedema.

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<sup>2</sup> More recent experience indicates that thyrotropic activity may occasionally be found in the serum of normal rabbits, and that it is not confined alone to those which have been thyroidectomized.

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## A PRELIMINARY REPORT ON THE VALUE OF STOCK VACCINE IN THE TREATMENT OF PNEUMONIA<sup>1</sup>

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For the last twenty years Wynn (1936) has advocated the treatment of pneumonia by the injection of stock vaccine. He has stated that by the use of vaccine he could obtain a definite reduction in the mortality of pneumonia, particularly if cases were treated within the first three days of the disease. The present communication is a preliminary report of our investigation, which is still in progress.

The sputum from all pneumonias admitted to the Royal Melbourne Hospital from April 1936 was cultured and a vaccine prepared containing *Pneumococci*, types I, II and III, a representative type IV, representative *Streptococci* and *Micrococcus catarrhalis*. Wynn was followed with regard to dosage, one cubic centimetre of the vaccine containing 600 million organisms equally partitioned between the six different types of organism. It was decided to limit the cases treated with vaccine to those admitted within the first three days of the disease. This was done, as it was only in this period that Wynn had any marked success, and in addition, after this time it is difficult to distinguish between a normal crisis and one due to the vaccine. Following Gaskell (1931), no distinction was made between lobar- and broncho-pneumonia—the only essential demanded being that the pneumonia should be primary and not secondary to any other condition. In many cases, at the time of administration of the vaccine, it would have been impossible to decide to which type the pneumonia belonged. Criteria for diagnosis consisted of a suggestive history and clinical signs of consolidation. If signs were absent or doubtful the diagnosis was confirmed by radiological examination.

It was a little more difficult to decide the method of assessing the value of the vaccine. If Wynn's figures are examined it will be seen that there are no control cases in his series. It is well known that mortality in pneumonia is very variable both at different periods and in different localities, and although he assumes a normal mortality of 20 per cent., much lower mortalities have been published, for example, Ryle and Waterfield's (1933) 154 cases with a mortality of 16 per cent. It is probably unfair to compare Wynn's results with this, but it is interesting to note that there is no statistically significant difference between a mortality of 11.5 per cent. with 320 cases and a mortality of 16 per cent. with 154 cases (Appendix I). This aspect is stressed to show the difficulty in drawing conclusions from mortalities even with a moderately

<sup>1</sup> Received October 26, 1937.

large number of cases. Similar remarks apply to the occurrence of complications. It is obvious that in a small series such as this, the basis chosen for comparison must be capable of showing a much greater proportional variation as the result of vaccine than that shown by mortality. In this connexion the duration of the disease was considered the most convenient for comparison. Criteria of onset were the times of development of the more dramatic symptoms: pleurisy, rigor, and shortness of breath. The cessation of infection was taken to be indicated by the return of temperature to the normal level, associated with distinct clinical improvement. No notice was taken of subsequent slight rises of temperature provided that the improvement was maintained. Daily differential white-cell counts were performed on a large number of the cases, primarily to obtain some idea of the changes to be expected in pneumonia, and also in the hope that some information as to the reasons for success or failure with vaccine therapy might become evident.

The routine attempted in each case was as follows: the patient was admitted to the ward and examined; a leucocyte count and blood films were taken and a specimen of sputum obtained for typing of organisms. If the diagnosis were considered definite and there were no contra-indications, one cubic centimetre of the vaccine was injected subcutaneously; if the diagnosis were uncertain the patient was taken to the Radiological Department and consolidation confirmed by fluoroscopic examination—if still doubtful, skiagrams were taken. In the early cases a second leucocyte count with differential count was performed one hour after the administration of the vaccine. This procedure was discontinued as it gave little, if any, additional information. A daily differential count was then performed, but as an improved understanding of the expected changes was obtained the period of examination was gradually extended. It was originally intended to vaccinate alternate patients, but owing to many cases not being reported within the three-day period the control series is considerably the larger of the two. This inequality does not affect the accuracy of the final results, but limits the sensitivity of the experiment. More important is the fact that the decision as to which cases receive vaccine has not been left entirely to chance—that is, perfect random sampling has not been obtained. This could have been obtained had the cases been selected by means of a table of random sampling numbers; alternatively a pack of cards could have been used, and after arranging them in random order by repeated shuffling the selection could have been made according to the colour of the suit chosen in each case. Actually, selecting alternate cases would have failed to give anything like complete random sampling. The element of chance in this experiment is fairly high, as apart from the limits described above, no actual selection of cases was made. Whether or not a case received vaccine depended on its being admitted to a ward whose resident medical officer was interested enough immediately to report the case. The result of this was that the majority of cases came from the same wards, the remaining wards providing the controls. The material consists of 168 cases of primary pneumonia admitted to the

wards from May 1936 to July 1937. Of these cases, 91 were admitted within the first three days of the disease, and of these 91 cases, 32 received vaccine therapy. The series is small, but the results appear to be sufficiently encouraging and the subject of sufficient importance to warrant these preliminary statements.

### Results

The results are best shown in tabular form for purposes of comparison.

Period when admitted.		Within first three days.		After first three days.	Total series.
		Vaccine series.	Control series.		
Mortality	Deaths	6	13	20	39
	Per cent.	18.8	22.0	26.0	23.2
Total compli- cations	Number	7	12	22	41
	Per cent.	21.9	20.3	28.6	24.4
Complications with recovery	Number	5	8	15	28
	Per cent.	15.6	13.6	19.5	16.7
Number of cases		32	59	77	168

It can be easily proved that, with the number of cases concerned, any differences in the above table might readily have occurred as the result of chance and are therefore of no value in assessing the value of the vaccine (Appendix II).

Turning to the duration of uncomplicated cases:—

	Mean $\pm$ standard deviation of mean.
Mean duration of control series in days	8.74 $\pm$ 0.61
Mean duration of vaccine treated series in days	5.69 $\pm$ 0.58
Difference in duration between the two series in days	3.05 $\pm$ 0.85

This difference in duration, even with the limited number of cases, can be proved to be significant (Appendix III). If perfect random sampling had been obtained the difference could have been ascribed to the effect of the vaccine. As it stands there is still some doubt as to the validity of this inference. Because of the possible criticism that the two series may have been unequal in the proportion of cases of different bacterial type, different age-period, or different seasonal incidence, these factors have been statistically excluded and in each case the difference in duration was found to be still highly significant (Appendix IV). The only other point brought out by this procedure was the possibility that the vaccine was ineffective in Type I pneumonia, but there are insufficient cases to prove this. The above method suffers from the disadvantages that it is impossible to include deaths and probably unfair to include complications in the comparison. On examination of the results it was found to be of very rare occurrence for the duration of untreated cases to be shorter than five days. It was therefore considered reasonable to compare the two series on the basis of whether or not the duration was less than this

period. By this means both complications and deaths could be included. When this is done by means of a contingency table, a highly significant index of dispersion is obtained, indicating that the vaccine treated series is more likely to recover within five days than the control series. The same remarks as regards random sampling apply equally in this test of significance (Appendix V). Even these results do not give a complete picture of the

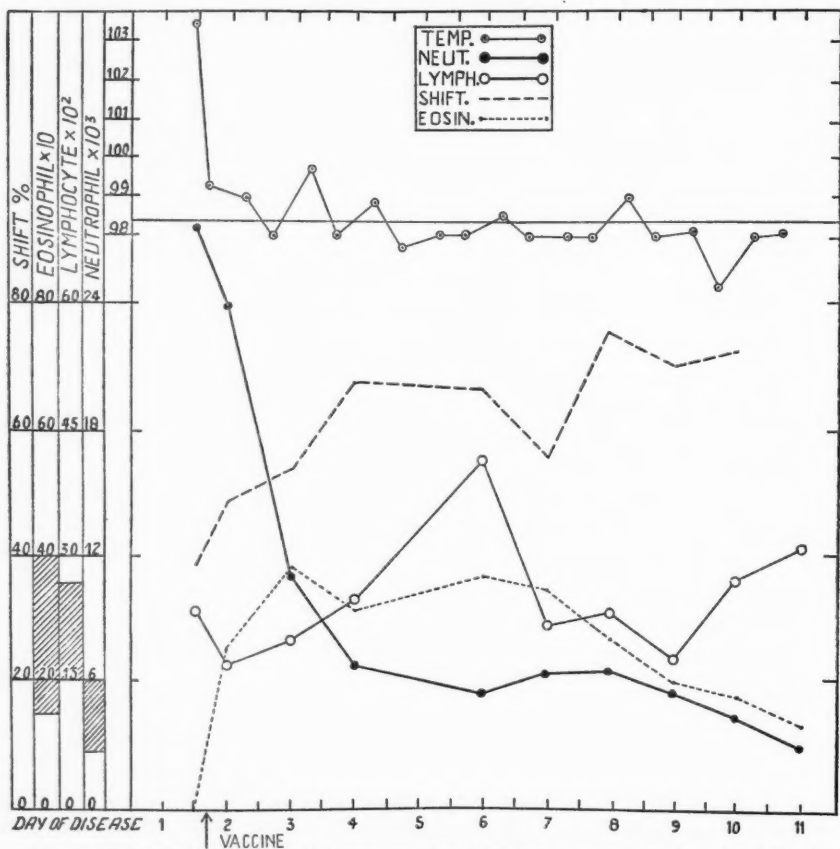


FIG. 1. Records of a patient with pneumonia of eighteen hours' duration who, following vaccine, had an immediate fall of temperature with marked clinical improvement within twelve hours. The infecting organism was a Type II Pneumococcus. Consolidation was radiologically confirmed the following day.

Note the absence of lymphopenia and the typical 'recovery picture'.

The shaded areas in the side columns show the normal ranges of the cells.

value of the vaccine. Six of the cases showed an immediate fall of temperature with dramatic clinical improvement within twelve hours of the administration of the vaccine. Three of these cases had a duration of less than three days. It was interesting to note that in the cases responding immediately to the vaccine, clinical signs followed their usual course—in one patient tubular breathing did not become evident until after the temperature had

returned to normal. In spite of the signs of consolidation these patients felt and looked well. It is results such as these, much more than any statistical analysis, that make one feel that the vaccine is effective. A patient comes in with a typical pneumonia, is given vaccine, and in twelve hours has a normal temperature which remains normal in spite of clinical and radiological evidence of consolidation (Fig. 1)—it is difficult to believe that this can be due to anything but the vaccine. Admittedly an occasional pneumonia will do this without treatment (two cases in the control series), but in these cases the signs were not extensive, although definite, and in both they did not follow their usual course, but almost immediately showed resolution. The number of these cases is small, but is significantly greater than that occurring in the control series. It would therefore seem that vaccine has the power of producing an immediate crisis in certain cases—the problem being why it does not produce the same effect in others.

#### *Discussion*

When the reputation of any form of therapy rests on small differences or depends on fairly striking successes in a comparative minority of cases, its value can be assessed only by a statistical comparison with an adequate control series. This statement applies particularly to vaccine in the treatment of pneumonia, as the majority suffering from this condition recover and probably would do so no matter what the treatment; and it would also appear that sudden improvement only occurs in a few, as yet unspecified, cases. The discussion must therefore centre round the statistical methods employed in the investigation and the validity of the conclusions drawn from them. This may be considered under three main heads—the number of cases in the investigation, the method of selection of the cases, and the statistical methods employed in analysing the results. With regard to the number of cases it might be argued that the series is too small to prove anything. This is admitted in connexion with mortality and occurrence of complications, but it must be taken, almost as an axiom, that the number of cases necessary to prove any particular phenomenon depends largely on the nature of that phenomenon: the more striking and the more uniform the results of a particular treatment, the fewer are the cases necessary to indicate the effectiveness of that treatment. No form of knowledge is absolutely certain—there is always the ‘million to one chance’—which means that the only measure of certainty that we have is in terms of the probability of a particular event occurring as the result of chance. All of us are inclined to consider as reasonably certain phenomena which may occur as the result of chance much more frequently than once in a million times—what then are we to take as a basis for reasonable certainty? Statisticians arbitrarily consider a probability of one in twenty as their basis, and although this may be sufficient in many cases it must also depend on the phenomenon which is being investigated. The probability of occurrence as the result of chance of one in twenty might be sufficient to encourage us to give a case of pernicious

anaemia intramuscular liver extract, but, because of the danger, we would require a much smaller probability in any published series of results before we would consider advising splenectomy for the condition. Vaccine, with the possible exception of its use in cases with a history of chronic cough, belongs to the former category. If we are, then, prepared to accept probabilities as a basis, we must therefore accept any number of cases which are sufficient to demonstrate that probability.

The methods used in determining probability are mathematical in origin, and without a mathematical training must, to some extent, be taken on trust. The principles used in this investigation were obtained from Fisher (1936, 1937) and Pearl (1930). Statistical results depend for their validity on chance being placed in complete control of the experiment. Much has already been said on the subject of random sampling, and although perfection could not be obtained in this direction, the means of selection of cases appears to be such as to give results taken fairly at random. This seems to be true for such causes of variation as age, season, and bacterial type, since exclusion of these still gives a probability of occurrence by chance of less than one in one hundred. It seems reasonable to assume that the other unknown factors which might possibly influence the course of pneumonia have been equally well scattered at random, particularly as the fact that they are unknown excludes the likelihood of unconscious selection. Hence these results can be taken to be true to an extent indicated by a probability somewhere in the region of that calculated.

My thanks are due to the Medical Staff of the Royal Melbourne Hospital for their kindness in supplying clinical material and for their permission to use hospital records; to Dr. S. V. Sewell and Dr. C. H. Kellaway for their help, criticism, and encouragement throughout the investigation; and to Dr. Hilda J. Gardner and other members of the Pathology Department for enthusiastic co-operation in the preparation of vaccine, staining of blood films, and performance of leucocyte counts. I am indebted to Dr. Mildred Barnard, Ph.D. (London), for the statistical method used in eliminating the effect of age, season, and type from the experiment, and for checking the remaining statistical procedures; and to Dr. A. D. Matheson for the preparation of the diagram.

#### *Conclusions*

1. Vaccine treatment appears to be successful in reducing the duration of uncomplicated pneumonia by an average of three days with a standard deviation of the mean of 0.85 days.
2. This appears to be so, even after the exclusion of age, seasonal severity, and bacterial type as causes of variation.
3. Recovery within five days of the development of pneumonia appears to be much more likely if vaccine has been administered.
4. Certain cases seem to respond immediately to vaccine with crisis and marked improvement of clinical condition.

5. It appears that there is some risk in administering large doses of vaccine to patients who, prior to the development of pneumonia, give a history of chronic cough.

# APPENDICES

## STATISTICAL TREATMENT OF RESULTS

### I

#### *Comparison of Mortalities. Wynn and Ryle & Waterfield.*

Author.	Died.	Lived.	Total.	Mortality.
Wynn	37	283	320	11.5 %
Ryle & Waterfield	25	129	154	16.0 %
Total	62	412	474	

$$\begin{aligned} \text{Index of dispersion using Yates' correction for continuity} &= \frac{(283 \times 25 - 129 \times 37 - 237)^2 \times 474}{62 \times 412 \times 154 \times 320} \\ &= 1.606. \end{aligned}$$

The probability of a difference as great as, or greater than, this occurring as the result of chance is in the region of 0.2. The difference in mortalities cannot be taken as significant.

### II

#### *Comparison of Mortalities and Incidence of Complications in the Present Series*

	Died.	Lived.	Total.	Mortality.
Control	13	46	59	22.0 %
Vaccine	6	26	32	18.8 %
Total	19	72	91	

$$\begin{aligned} \text{Index of dispersion using Yates' correction} &= \frac{(26 \times 13 - 46 \times 6 - 45.5)^2 \times 91}{19 \times 72 \times 32 \times 59} \\ &= 0.00959 \end{aligned}$$

The probability of this difference occurring as the result of chance is about 0.95. The difference is therefore not significant. The difference in incidence of complications is less than that for mortalities, and with the same number of cases must be similarly of no significance.

### III

#### *Comparison of Duration of Uncomplicated Cases in the Two Series*

##### A. CONTROL SERIES

Duration in days.	Frequency <i>f</i> .	Deviation <i>d</i> .	<i>fd</i> .	<i>fd</i> <sup>2</sup> .
4-5	2	-4	-8	32
5-6	6	-3	-18	54
6-7	8	-2	-16	32
7-8	3	-1	-3	3
8-9	5	0	-45	—
9-10	2	+1	+2	2
10-11	6	+2	+12	24
11-12	1	+3	+3	9
12-13	3	+4	+12	48
18-19	1	+10	+10	100
23-24	1	+15	+15	225
	38		+54	529
			-45	
			+9	

## III (continued)

Assumed mean	= 8.50 days
Correction	= + 0.2368
True mean	= 8.7368 days
Sum of squares	= 529
Correction	= - 2.131
True sum of squares	= 526.869
Variance	= 14.24
Variance corrected for grouping	= 14.16
Standard deviation	= 3.762
Sampling variance of mean	= 0.3747
Standard deviation of mean	= 0.6122
Mean duration of control series in days	= 8.74 ± 0.61

## B. VACCINE TREATED SERIES

Duration in days.	Frequency <i>f</i> .	Deviation <i>d</i> .	<i>fd</i> .	<i>fd</i> <sup>2</sup> .
1-2	2	-4	-8	32
2-3	1	-3	-3	9
3-4	3	-2	-6	12
4-5	2	-1	-2	2
5-6	4	0	= -19	—
6-7	3	+1	+3	3
7-8	3	+2	+6	12
8-9	1	+3	+3	9
9-10	1	+4	+4	16
12-13	1	+7	+7	49
	21		+23	144
			-19	
			+4	

Assumed mean	= 5.50 days
Correction	= + 0.19
True mean	= 5.69 days
Sum of squares	= 144
Correction	= - 0.76
True sum of squares	= 143.2
Variance	= 7.16
Variance corrected for grouping	= 7.08
Standard deviation	= 2.66
Sampling variance of mean	= 0.341
Standard deviation of mean	= 0.58
Mean duration of vaccine treated series in days	= 5.69 ± 0.58
Difference in duration	= 3.046 days

Standard deviation of the difference =  $\sqrt{(0.3746 + 0.3410)}$   
= 0.8461

Difference in duration is therefore 3.046 ± 0.8461

$$t = \frac{3.046}{0.8461} = 3.60.$$

The number of degrees of freedom is 57, two less than the total number of cases. Since this is well over 30 it is reasonable to use values derived from the normal curve to estimate the probability of a difference as great as, or greater than, this occurring as a result of chance. The probability lies between 0.04 and 0.03 in 100 trials, and it is therefore highly unlikely that such a difference could occur as the result of chance. Hence the populations are different, either originally or as a result of the difference in treatment between the two groups.

## IV

*Elimination of Effects of Age, Season, and Type on the Duration of the Uncomplicated Cases*

		AGE				
	Range in years.	Duration in days.	Number of cases.	Total.	Mean.	Sum of squares.
Vaccine series.	10-20	3, 5, 6, 7	4	21	5.25	119
	20-30	1.5, 1.5, 2, 3.5, 4, 5, 5, 6, 6, 12	10	46.5	4.65	302.75
	30-40	4, 5, 8	3	17	5.66	105.0
	40-50	7, 7	2	14	7.00	98.0
	50-60	3, 7	2	10	5.00	58
Control series.	10-20	6, 10, 12	3	28	9.33	280
	20-30	5, 5, 6, 6, 8, 9, 23	7	62	8.86	796
	30-40	4, 5, 6, 6, 7, 7, 8, 9, 10, 10, 10, 12	12	94	7.83	800
	40-50	6, 6, 8, 12, 18	5	50	10.00	604
	50-60	4, 5, 6, 8, 10, 10, 11	7	54	7.71	462
Total		—	55	—	—	590.57

 Estimate of the variance of a single duration ( $s^2$ )

$$\begin{aligned}
 &= \frac{590.57}{55 - 10} \\
 &= 13.1237
 \end{aligned}$$

## DIFFERENCES IN DURATION IN EACH AGE-PERIOD

Range.	Difference.	Variances.	Reciprocal.
10-20	4.08	$s^2(\frac{1}{4} + \frac{1}{3}) = 0.5833 s^2$	1.714
20-30	4.21	$s^2(\frac{1}{10} + \frac{1}{7}) = 0.2429 s^2$	4.117
30-40	2.17	$s^2(\frac{1}{3} + \frac{1}{12}) = 0.4166 s^2$	2.400
40-50	3.00	$s^2(\frac{1}{4} + \frac{1}{2}) = 0.7000 s^2$	1.427
50-60	2.71	$s^2(\frac{1}{2} + \frac{1}{7}) = 0.6429 s^2$	1.556
Total			11.216

Weighted mean of differences

$$= \frac{\frac{4.08}{0.5833} + \frac{4.21}{0.2429} + \frac{2.17}{0.4166} + \frac{3.0}{0.7} + \frac{2.71}{0.6429}}{11.216} = 3.391.$$

 Variance of weighted mean =  $\frac{13.12}{11.22} = 1.169$ .

Standard deviation = 1.081

$$t = \frac{3.391}{1.081} = 3.137.$$

$$n = 45.$$

Probability is less than 0.01.

SEASONAL EFFECT							
	Season: periods of three months.	Duration in days.	Number of cases.	Total.	Mean.	Sum of squares.	Corrected sum of squares.
Vaccine series.	First	1, 5, 3, 3, 3-5, 5, 6, 7, 7, 8, 12	10	56-0	5-60	399-50	85-90
	Second	4, 5, 6, 7	4	22-0	5-50	126-00	5-00
	Third	2, 4, 5, 5, 6	5	22-0	4-40	106-00	9-20
	Fourth	1-5, 7	2	8-5	4-25	51-25	15-12
Control series.	First	4, 5, 5, 6, 6, 6, 7, 8, 8, 10, 10 10, 11, 12	14	108	7-71	916-00	82-86
	Second	4, 5, 5, 6, 6, 7, 8, 8, 9, 10, 10, 12, 12, 18, 23	15	143	9-53	1737-00	373-73
	Third	5, 6, 6, 6, 9, 10	6	42	7-00	314-00	20-00
	Fourth	5, 7, 8	3	20	6-67	138-00	4-67
Total		—	59	—	—	—	596-48

Estimate of the variance of a single duration ( $s^2$ )

$$= \frac{596-48}{59-8}$$

$$= 11-6957.$$

#### DIFFERENCES IN SEASONAL INCIDENCE

Season.	Difference.	Variances.	Reciprocal.
First	2-11	$s^2(\frac{1}{16} + \frac{1}{14}) = 0-1714 s^2$	5-8333
Second	4-03	$s^2(\frac{1}{4} + \frac{1}{17}) = 0-3167 s^2$	3-1579
Third	2-60	$s^2(\frac{1}{3} + \frac{1}{4}) = 0-3667 s^2$	2-7272
Fourth	2-42	$s^2(\frac{1}{2} + \frac{1}{3}) = 0-8333 s^2$	1-2000
Total			12-9184

Weighted mean of differences

$$= \frac{\frac{2-11}{0-1714} + \frac{4-03}{0-3167} + \frac{2-60}{0-3667} + \frac{2-42}{0-8333}}{12-92} = 2-706.$$

Variance of weighted mean =  $\frac{11-70}{12-92} = 0-9055.$

Standard deviation = 0-9517

$$t = \frac{2-7140}{0-9515} = 2-84.$$

$$n = 51.$$

Probability is less than 0-01.

TYPE OF INFECTING ORGANISM  
 (Judged by predominating organism in sputum)

	Type.	Duration in days.	Number of cases.	Total.	Mean.	Sum of squares.	Corrected sum of squares.
Vaccine series.	Pn. I	6, 7, 8, 10, 12	5	43	8.60	393	23.2
	Pn. II	1.5	1	1.5	1.50	2.25	0
	Pn. IV	2, 4, 5, 5, 5, 5,	8	39	4.875	205.00	14.9
	6, 7						
	<i>Strep. haem.</i>	3.5, 6	2	9.5	4.75	48.25	2.1
Control series.	<i>Strep. viridans</i>	7	1	7.00	7.00	49.00	0
	Pn. I	4, 6, 8, 9, 10, 10	7	57.00	8.143	497.00	32.9
	Pn. II	5	1	5.00	5.000	25.00	0
	Pn. IV	5, 5, 6, 6, 8, 9, 12	7	51.00	7.286	411.00	39.4
	<i>Strep. haem.</i>	6, 7	2	13.00	6.500	85.00	0.5
	<i>Strep. viridans</i>	18, 23	2	41.00	20.500	853.00	12.5
	Total	—	36	—	—	—	125.5

 Estimate of the variance of a single duration ( $s^2$ )

$$= \frac{125.5}{36 - 10}$$

$$= 4.827.$$

## DIFFERENCES IN TYPE

Type.	Difference.	Variance.	Reciprocal.
Pn. I	-0.457	$s^2 (\frac{1}{3} + \frac{1}{7}) = 0.3429 s^2$	2.917
Pn. II	+3.500	$s^2 (\frac{1}{1} + \frac{1}{1}) = 2.0000 s^2$	0.500
Pn. IV	+2.411	$s^2 (\frac{1}{3} + \frac{1}{7}) = 0.2679 s^2$	3.733
<i>Strep. haem.</i>	+1.750	$s^2 (\frac{1}{2} + \frac{1}{2}) = 1.0000 s^2$	1.000
<i>Strep. viridans</i>	+13.500	$s^2 (\frac{1}{1} + \frac{1}{2}) = 1.5000 s^2$	0.667
		Total	8.817

Weighted mean of differences

$$= \frac{\frac{3.5}{2} + \frac{2.411}{0.2679} + \frac{1.75}{1} + \frac{13.5}{1.5} - \frac{0.457}{0.3429}}{8.817} = 2.288.$$

$$\text{Variance of weighted mean} = \frac{4.827}{8.817} = 0.5474.$$

$$\text{Standard deviation} = 0.7399$$

$$t = \frac{2.288}{0.7399} = 3.091.$$

$$n = 25.$$

Probability is less than 0.01.

## V

*Comparison of the Two Series on the Basis of Recovery Within Five Days*

	Recovery within five days.	No recovery within five days.	Total.
Control series	2	57	59
Vaccine series	8	24	32
Total	10	81	91

$$\begin{aligned}
 \text{Index of dispersion using Yates' correction for continuity} &= \frac{(456 - 48 - 45 \cdot 5)^2 \times 91}{10 \times 81 \times 32 \times 59} \\
 &= \frac{362 \cdot 5^2 \times 91}{10 \times 81 \times 32 \times 59} \\
 &= 7 \cdot 818.
 \end{aligned}$$

The odds against this value being exceeded by chance are approximately 190 to 1.

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## HYPOGONADISM ASSOCIATED WITH INVASION OF THE MID-BRAIN AND HYPOTHALAMUS BY A PINEAL TUMOUR<sup>1</sup>

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With Plates 12 to 15

### *Introduction*

TESTICULAR atrophy is a sufficiently rare phenomenon to excite attempts to explain it, yet histological studies of the genital organs in such instances are rare. Those cases not attributable to inflammatory causes are apt to be ascribed to pituitary dysfunction. While this interpretation is likely to be correct in many instances, the mechanism by which the changes are brought about remains unexplained. Our limited knowledge of this condition demands a careful microscopic examination of the tissues concerned if a full understanding is to be achieved concerning the dependence of the gonads on the pituitary. This relationship, so long suspected on clinical and pathological grounds, has been unquestionably established by experiment. The regression of sex glands and characters which follow hypophysectomy (Crowe, Cushing and Homans, 1910; Aschner, 1912; Smith, 1927*b*, 1930), their restoration by replacement therapy (Smith, 1927*b*, 1930) and the stimulation of the immature animal to precocious sexual development (Zondek and Ascheim, 1926; Smith, 1927*a*) constitute the outstanding evidence. While this demonstration of the humoral mechanism by which the pituitary controls the reproductive and other endocrine glands is of fundamental importance, appreciation of the details of pituitary function is far from complete. Consequently it is still most difficult to interpret in terms of pituitary activity changes observed in many clinical conditions in which the pituitary is suspected of playing a part. In time, no doubt, the rapid advances which are being made in this field will lead to fuller comprehension, but until recently, at least, the multitude of facts disclosed by research has complicated rather than clarified the situation. Pre-eminent amongst these facts is the demonstration of the high degree of interdependence of the pituitary and its neighbouring nervous structure in the diencephalon in virtue of both the nervous (Greving, 1926; Pines, 1926; Beattie, 1932; Clark, 1936) and vascular connexions (Popa and Fielding, 1930; Wislocki and King, 1936). Lesions affecting the hypothalamus may, therefore, give rise to disturbed

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pituitary function. Conversely, changes in the pituitary may give rise to symptoms generally attributed to disturbed function of the hypothalamic centres. Assignment of such symptoms as adiposity or polyuria on a unitarian basis is impossible at present. The pituitary and its connexions must be considered as a functional unit. While the pituitary-hypothalamus relationship is but little understood, the function and source of the multiplicity of hormones assigned to the hypophysis are no less difficult to interpret. In so far as the pituitary gonadotropic fraction is concerned, it is by no means established whether there are one or more hormones and from what cell type or from what part of the adenohypophysis they originate. Similar uncertainty exists for the testes. Such questions present themselves in the case to be related, in which evidence of disturbed pituitary function is found as the indirect result of a tumour of the pineal gland which invaded the brain stem causing hydrocephalus.

#### *Case Report*

C. W., male, aged 23, was admitted to the Toronto General Hospital on March 22, 1936.

*History of illness (obtained from the patient):* In January, 1935, he first experienced double vision which persisted, gradually becoming worse. During the following year he felt nervous and depressed, and during the latter six months suffered frequent severe throbbing headaches behind the left eye. In December, 1935, while out of a job and penniless, he attempted suicide by drowning, but was rescued by the police. Three weeks before admission a burning ache commenced in the soles of his feet and gradually extended to the knees. For the last week he was confined to bed and the legs felt as if paralysed. Recently he had been unable to control bladder or bowel. Occasional 'dizzy spells' and 'singing' in the ears occurred, but the patient was unable to give any detailed account of these symptoms. He had lost thirty-seven pounds in weight during the past three years.

*Information obtained after patient's death from his mother in England and his various employers since coming to Canada:* Nothing unusual was noted during his early development in England. He did moderately well at school, but preferred the open-air life and came to Canada five and a half years ago as one of a group of boys sent out to learn farming. During the first two years he applied himself to the work and was considered quite satisfactory by his employers. The first evidence of anything unusual was contained in letters to his mother in 1932, where mention was made of an increasing tendency to sleep in the daytime which was entirely new to him. During 1933 this sleepiness became noticeable to his employers, and was associated with a lack of initiative which rendered him less efficient in his farm labours. He was reprimanded for laziness and finally discharged on this account, although it was stated that he was clean and tidy, thoughtful of others and had a pleasant personality. During 1934 and 1935 he was employed by various farmers, all of whom found his work very unsatisfactory. His mental alertness gradually decreased. He became less sociable, and in 1935 was quite noticeably dirty and untidy about his person. He would sleep whenever the opportunity offered and it was always difficult to get him up in the morning. During 1934 and 1935 his employers were all impressed by his tremendous appetite.

He was never satisfied, regardless of how much food was put before him, and on occasions would eat until he vomited. Despite the large quantities of food consumed he gradually lost weight. Towards the latter part of 1935 he became very depressed and would often burst into tears for no apparent reason. This was attributed to eye trouble of which he frequently complained. From January, 1936, he complained of severe frontal headaches, showed gradually decreasing initiative, and would fall asleep at once if left alone. In spite of eating excessively large meals he demanded food at all hours. At this time nightly incontinence of urine commenced, which was partly responsible for his discharge from his last job on January 27, 1936. From then until admission to hospital eight weeks later, he stayed at a boarding house where it was observed that he slept a great deal of the time. The sheets on his bed had to be changed frequently owing to the incontinence of bladder and bowel. During this time he masturbated a great deal, regardless of whether people were observing him. Difficulty in walking, which was attributed to pain in the feet, was first noted two weeks before admission and within a week of its onset he became confined to bed. No history definitely indicating polyuria was obtained from the patient or from the other informants.

*Examination:* The patient was a poorly nourished boy (height, 5 feet 6 inches; weight, 116 pounds) and appeared younger than his stated age. There was no inclination to talk spontaneously and his response to questioning was very slow and inadequate, suggesting marked retardation of thought. He was well orientated for time and place, but memory, perception and attention were all impaired. Emotionally he was depressed and was never seen to smile. At times he appeared apprehensive and was observed to tremble when a doctor approached his bed. In answer to questioning the patient stated that he had practised masturbation since the age of thirteen and had experienced a deep sense of shame regarding it. Attempts to abstain had never been successful for very long. The act was always preceded by thoughts about the opposite sex. He said that girls had never liked him, which he attributed to his failure to grow a beard, and he was obviously very perturbed about the lack of masculinity in his appearance. The hair on his scalp was profuse and fine in texture. The patient had never shaved and there was only a fine down on the upper lip and a few fine hairs on his chin. Pubic hair was present in about normal amount, but of feminine type in distribution. Axillary hair was fine and scanty. There was no hair on the chest and very little on the extremities. The penis was of average size, but the testes were very small, being about the size of small marbles. In reply to questioning regarding the size of the testes, the patient stated that they had been getting smaller since the age of seventeen years at which time they were the size of walnuts. Oedema was present over the dorsa of both feet, extending half-way up to the knees. The feet were red and excoriated. The skin over the toes was dusky red in colour, wrinkled and quite tender on pressure. This condition in the lower limbs was diagnosed as epidermophytosis with secondary infection.

Examination of the heart, lungs, and abdomen revealed nothing grossly abnormal. The blood-pressure was 128/52. Appreciation of smell was present in both nostrils. The fundi showed nothing abnormal apart from some blurring of the margin of the right disk at the upper pole. There was also some fullness of the veins in this region. Vision was 6/12 in both eyes. The visual fields were full for form and colour. No limitation of ocular movements was detected. Diplopia was present in variable degree on lateral deviation to both sides when the test object was about three feet from the eyes. However,

examination with a red glass showed no external ocular paralysis apart from a weakness of the left external rectus muscle. The pupils were large and approximately equal in size. They did not react to light directly or consensually, but did react on convergence. The examination of the remaining cranial nerves revealed no abnormality. The hands were cold and slightly cyanosed. Power was fair and equal in the two upper limbs. Tests for co-ordination were carried out very slowly, but accurately. No alteration in tone or sensation was detected. The tendon reflexes in the arms were present and equal, but sluggish. The abdominal muscles contracted well and the abdominal and cremasteric reflexes were present and equal. Examination of the lower limbs showed that he was unable to move his right leg at the hip, knee, or ankle, or to move the toes. He moved the left leg on several occasions, but the movements were all very weak. He complained that movement caused pain in the legs, and it was difficult to be sure how much of the weakness in the legs was real and how much was due to lack of co-operation. However, the right leg was not withdrawn when painful stimulation was applied whereas the left leg was drawn back. No definite disturbance of tone was detected in the lower limbs on passive movement. Tests for superficial and deep sensation in the lower limbs revealed no abnormality, but co-operation was poor. The tendon reflexes in the legs were present and equal, but very sluggish. The plantar reflexes were difficult to test because of marked tenderness of the soles of both feet and no conclusive response, either of dorsiflexion or plantar flexion, was obtained.

*Laboratory findings:* Urine analysis negative. Blood examination: haemoglobin 80 per cent; red-cell count 5,100,000; white-cell count 7,200; smear, normal; Wassermann negative. Sugar tolerance test (100 gm. glucose) gave the following results:

Time.	Blood-sugar.	Sugar in urine.
Fasting	0.091 %	0
$\frac{1}{2}$ hour	0.128 %	(no specimen)
1 hour	0.155 %	0
2 hours	0.069 %	(no specimen)
3 hours	0.069 %	0

Basal metabolic rate normal. Cerebrospinal fluid clear; pressure 200 mm.; Pandy 2+; cell count 16 per c.mm., all mononuclears; Wassermann and Kahn tests negative; colloidal gold reaction normal. X-ray examinations of the skull showed the pineal shadow to be in the midline and somewhat larger and more dense than usual. There was definite thinning of the posterior clinoid processes, but otherwise nothing abnormal was noted.

*Progress:* Under observation in hospital for four and a half weeks the patient's condition remained fairly stationary, except that the left leg gradually became paralysed to the same extent as the right. The inflammatory condition in the legs improved rapidly under treatment. He slept a large part of the time, taking no interest in his surroundings or in the other patients in the ward. He ate voraciously all the food that was given to him. There was incontinence of bladder and bowel and the patient would make no effort to notify the attendants when the sheets were soiled. He masturbated repeatedly, at times in full view of the ward, and when urged to stop replied that he could not help it. The temperature was elevated to 100° F. daily during the first week in hospital, then showed occasional elevation for three weeks and finally, during the last four days, it fluctuated between 99.4° and 103°. The pulse-rate was not remarkable, varying with the temperature.

Respirations were normal. On April 23, while being lifted into a chair, he suddenly lost consciousness and showed generalized convulsive movements of the limbs. Seen shortly afterwards, the breathing was stertorous, the patient was deeply cyanosed and the head and eyes were deviated to the left. The pupils were small and inactive, and all four limbs were flaccid. No tendon reflexes could be elicited, except the left ankle jerk. There was bilateral dorsi-flexion on plantar stimulation. After about fifteen minutes the pulse, which was feeble and irregular, became imperceptible and respirations ceased.

*Final clinical diagnosis:* Cerebral tumour involving the brain stem and extending forward into the hypothalamic region, with an associated internal hydrocephalus.

#### *Post-mortem Examination*

The external appearance of the body was as described in the clinical report. A complete autopsy was done and massive pulmonary embolism was found as the immediate cause of death. It was thought that these emboli had originated in the large veins of the pelvis or in the femoral veins, but no remnants of thrombus material were found in these veins as proof of this theory. With the exception of brain and endocrine glands, the organs were essentially normal. The following description, therefore, will be confined to the organs of special interest in relation to the endocrine dysfunction.

*Brain.* Gross examination: The calvarium and the underlying dura mater were normal. Exposure of the brain showed flattening of the convolutions uniformly distributed over both cerebral hemispheres. Removal of the brain showed the diaphragma sellae to be depressed and the underlying pituitary gland was seen, after removal, to be somewhat flattened from above downwards. The posterior clinoid processes were atrophied. The spinal cord showed no abnormality. The large vessels at the base of the brain were small, but their walls and their distribution were normal. The floor and the anterior wall of the third ventricle were extremely distended and thinned (Plate 12, Fig. 1), the mammillary bodies being flattened out at the posterior extremity of the distended floor of the ventricle. The pons showed some arched deviation of its midline to the left. It was firm on palpation, but showed no gross abnormality of its contour. The left cerebral hemisphere was slightly wider than the right and had a more rounded, bulging surface. A sagittal section cut between the two cerebral hemispheres split the midbrain and pons slightly to the right of their mid-sagittal planes, with the result that the pineal gland and its adjacent structures lay wholly in the left half of the specimen. The left half of the brain was sacrificed for histological investigation, the right half being preserved intact (Plate 12, Fig. 1). The cut surface showed a large greyish-white tumour of a somewhat spongy texture occupying the dorsal portion of the midbrain and extending forward to bulge the posterior wall of the third ventricle. The tumour measured 4.5 cm. antero-posteriorly and 2 cm. in the vertical plane. It contained numerous large, smooth-walled, cystic cavities filled with clear yellow fluid. The superior and inferior colliculi were pushed backwards by the tumour and apparently were infiltrated by it. The pineal gland occupied its normal position immediately above and between the superior colliculi. It was larger than normal, measuring 1 cm. in its transverse diameter and 0.6 cm. in its vertical diameter. The centre of the gland was filled with calcified material, forming an oval nodule

measuring approximately 0.5 cm. in diameter. The inferior surface of the gland was adherent to and apparently incorporated with the tumour in the underlying midbrain. The tumour tissue in the midbrain had compressed the aqueduct, causing severe obstructive hydrocephalus of the lateral and third ventricles. The ventricular distension is shown in Plate 12, Fig. 1. The cavity of the right lateral ventricle is exposed, as the section was cut to the right of the intact septum pellucidum. Both interventricular foramina were widened to a diameter of 0.7 cm. The illustration demonstrates the flattening by the pressure of the internal hydrocephalus of the tissues composing the floor of the third ventricle, including the optic chiasma and the mammillary bodies.

**Microscopical report:** A block of tissue cut through the calcified pineal gland and the underlying midbrain, including the cavity of the aqueduct, required decalcification. The pineal tissue surrounding the calcified centre of the gland was the seat of a tumour growth which consisted of an irregular proliferation of large epithelial cells containing centrally placed nuclei with a light chromatin content surrounded by a considerable quantity of cytoplasm. (Plate 12, Fig. 2.) These cells were reasonably typical of pineal parenchymal epithelium and showed some evidence of arrangement in lobular masses such as are generally found in normal glands. Scattered irregularly among these larger epithelial elements were masses of small, round cells with darkly staining nuclei and practically no surrounding cytoplasm. (Plate 12, Fig. 2.) These smaller elements have been described by Globus and Silbert (1931) as being present in normal young pineal glands, and it is suggested that they are parenchymal epithelial elements of an embryonic type. These two types of tumour cells passed directly from the pineal gland to invade the tissue of the underlying midbrain with no line of demarcation between the two structures. The larger epithelial elements spread directly into the nerve tissue, whereas the smaller elements tended to spread along perivascular spaces. Considerable numbers of multinucleated masses of cytoplasm consisting of imperfectly divided, large epithelial elements could be seen throughout the tumour tissue, but mitotic figures could not be found. A low power photomicrograph (Plate 13, Fig. 3) shows the margin of tumour infiltration of the midbrain tissue. The nerve tissue at the margin of the tumour contained moderate numbers of proliferating, hypertrophied astrocytes. The aqueduct was surrounded by tumour tissue. The lumen of the canal was somewhat compressed, but patent and surrounded by a normal ependymal epithelium. Fine granular deposits of calcium salts were present throughout the tumour tissue.

The tissue of the left hypothalamus was oedematous. Both types of tumour cells could be seen penetrating this tissue along perivascular spaces. Many of the hypothalamic nerve cells showed severe vacuolar degenerative changes in their cytoplasm. Sections through the lower midbrain and pons showed the tumour to be invading the upper pontine tissue to a slight extent. There was no evidence that it originated in ependymal epithelium. A section of cerebral cortex taken from the left frontal pole showed thinning of the cortical tissue. There was patchy atrophy of the nerve cells with disturbance of their layering, and many of them stained hyperchromatically. These cortical changes were probably secondary to the pressure of the internal hydrocephalus. The subcortical white matter showed severe oedema by marked acute swelling of oligodendroglia.

**Pituitary.** Gross appearance: The gland was somewhat flattened from above downwards by the pressure of the overlying, distended third ventricle. It was smaller than normal, weighing 0.4 gm. A horizontal section showed

no gross abnormality. Microscopical structure: The anterior lobe was intensely congested. Pars intermedia tissue was small in amount. The posterior lobe showed oedema, and small haemorrhages were found in this lobe. (Plate 13, Fig. 4.) The glandular cells showed some diminution in numbers of the acidophilic elements, but the cytoplasm of individual cells appeared to be well filled with granules. The basophile and chromophobe cells were normal in structure and in numbers. The gland was examined in serial microscopic sections and the histological appearances, as described above, were uniformly present.

*Testes and accessory sex organs.* Both testes were small. The right testis and epididymis together weighed 3 gm., (average 10.5 to 14 gm.). The testis measured  $2 \times 1.5 \times 0.7$  cm. (average  $5 \times 3 \times 2.5$  cm.). The left testis and epididymis together weighed 3.5 gm. This testis was not measured. Both testes were firmer than usual. Their cut surfaces were smooth, pale brown in colour and slightly translucent. The seminiferous tubules could not be teased out from the surface in the usual manner. Paraffin sections of the testes stained with haematoxylin and eosin revealed only remnants of seminiferous tubules occurring in small clusters at wide intervals. The basement membranes of many of the tubules showed marked thickening and hyalinization with complete loss of lining cells and obliteration of the lumina. In a few groups of tubules the basement membranes were only slightly thickened and partially hyalinized. The germinal epithelium in these was completely atrophied, the cells which remained consisting of Sertoli cells. (Plate 14, Fig. 5.) Many of these showed marked degenerative changes; some lay free in the lumen. Definite germinal cells could not be identified and none of the tubules contained spermatozoa. The small groups of seminiferous tubules were widely separated by loose fibrous stroma in which were masses of cells identified as interstitial cells of Leydig. (Plate 14, Fig. 6.) These occurred in large, rounded masses and formed the great bulk of the total testicular tissue. They appeared to be markedly increased in numbers in relation to the scattered groups of atrophic tubules. The Leydig cells were plump, with small, round, darkly staining nuclei and pale, finely granular, acidophilic cytoplasm. In frozen sections stained for fat with Sudan III, the cytoplasm of the interstitial cells was found to contain a sparse sprinkling of fine sudanophilic, fatty droplets. Some of the Sertoli cells lining the seminiferous tubules also contained a small number of fatty droplets, localized toward their bases. Other special stains of sections of the testes added no further information. A section of the epididymis showed the usual arrangement of the tubules which were lined by columnar, ciliated epithelium. (Plate 15, Fig. 7.) This appeared normal in all respects. The lumina were patent and contained only a small quantity of pink staining, finely granular material. Spermatozoa were completely lacking.

The prostate gland was of average size and normal shape. The urethra was patent and the verumontanum was not enlarged. The cut surfaces of the prostate showed a homogeneous tissue of pale, reddish-grey colour differing in no respect from the appearance of prostatic tissue in a young adult. The seminal vesicles were of normal size and presented the usual lobulated appearance. Laid open by longitudinal cuts they were found to be lined by a mucous membrane of normal appearance. The vas deferens was cord-like in structure with a distinctly patent lumen. Microscopical study of the prostate revealed no significant abnormalities in its structure. (Plate 15, Fig. 8.) The gland acini were arranged in the usual manner in a fibro-muscular stroma. The lining epithelium varied from low to moderately high columnar

type and appeared normal in all respects. Many of the gland acini contained clumps of finely granular, pink-staining material and a few desquamated epithelial cells. Some of the ducts near their points of opening into the urethra showed squamous metaplasia of their lining epithelium, but they appeared otherwise normal. A section of one seminal vesicle presented a lining epithelium which was entirely normal, with the exception of two minute areas where squamous metaplasia had occurred.

*Adrenal, pancreas, thyroid, and parathyroid glands.* The adrenal glands, carefully freed from all adherent fat, together weighed 9.5 gm. (average 17 gm.). Their external configuration was normal, and numerous transverse sections revealed no gross lesions. The cortex presented a uniform, bright yellow colour, and the grey medullary tissue was found in the usual quantitative proportion. Microscopic sections revealed cortical and medullary tissue of entirely normal appearance, with the exception of a small area at one extremity of one section in which the cortical tissue was atrophied and disorganized in arrangement. The islands of cortical cells remaining occurred in rounded clusters embedded in a loose, fibrous stroma and resembled remnants of the zona glomerulosa.

The pancreas weighed 75 gm., (average 60 to 100 gm.), and presented the usual gross appearance. The lobulated structure was distinct and uniform on numerous cut surfaces. In microscopic sections the acinar tissue appeared in no way remarkable. The islets of Langerhans were found in the usual numbers and were composed of well preserved cells in normal arrangement. The individual islets, however, were small.

The thyroid gland weighed 11 gm. (average 20–40 gm.) and presented the usual configuration with symmetrical lobes. No nodules were present and the cut surface presented a homogeneous, reddish, slightly translucent tissue. Microscopical examination revealed acini of fairly uniform size, well filled with homogeneous, pink-staining colloid and lined uniformly by cuboidal epithelium.

Three parathyroid glands were found. All of these were smaller than usual, the largest measuring only 3 mm. in its greatest diameter. Microscopical sections of these showed slight infiltration of the tissue by fat. The cells of the parenchyma appeared entirely normal; no eosinophilic cells were noted.

#### *Analysis of the Clinical Signs and Symptoms*

*Cerebral features:* Despite the block in the ventricular system and well-marked internal hydrocephalus found at autopsy, the clinical signs of increased intracranial pressure were surprisingly few. There was no gross papilloedema, and it was only a few months before death that severe headache became prominent. From this it would seem that the obstruction of the aqueduct of Sylvius by tumour and the consequent development of internal hydrocephalus occurred very gradually. This view receives support from the observations of Riddoch (1936) who has cited cases showing that when 'ventricular blockage is very slow and progressive but variable, the process extending over a period of months or years—headache, vomiting and papilloedema may be absent even at a stage when dementia or stupor, general enfeeblement and incontinence are advanced'. The patient's first complaint was drowsiness. This developed four years before death and suggested that the tumour was causing alteration in function of the structures

in the walls of the aqueduct or third ventricle at that time. Rowe (1935) has presented evidence against the view of a narrowly localized area in the central nervous system controlling the sleep rhythm. Following a review of the literature up to 1935 and a study of several cases, he concludes that 'disturbances of sleep result from lesions of a rather diffuse central correlating mechanism which may lie in the medial thalamic nuclei, or from the interruption of a thalamico-periventricular-hypothalamico-mesencephalic chain of neurones conducting impulses to or from such a mechanism'. In our case, the tumour was so situated that this pathway might have been involved directly from invasion of the region about the cephalic end of the aqueduct, or indirectly from damage to the structures in the walls and floor of the third ventricle resulting from blockage of the aqueduct. The early somnolence, which gradually increased, was probably caused by the former lesion. It was not until about two years after the onset that definite mental retardation was apparent, suggesting the development of marked internal hydrocephalus. Considering the degree of involvement of the midbrain by tumour, the paucity of signs and symptoms referable to this region, until shortly before death, is remarkable. Diplopia had been present for 14 months, but it was not until about three months before death that impairment of sphincter control was noted. At first bladder incontinence occurred only at night, but three weeks later the bowel became similarly affected and there was incontinence during the day as well. No symptoms of retention of urine were observed and the nature of the incontinence closely resembled that seen occasionally in patients with frontal lobe tumours (Hyland and Botterell, 1937). Apathy and lack of initiative were probably important in causing the incontinence, particularly during the first few weeks it was present. However, in view of the evidence found later on examination that the motor pathways to the lower limbs were involved, it is possible that the deeply infiltrating midbrain tumour contributed directly to the sphincter disturbance. It has been shown experimentally that electrical stimulation in the hypothalamus causes alteration in bladder tonus (Beattie and Kerr, 1936; Kabat, Magoun and Ranson, 1936). As yet there is no experimental evidence available for localized control of bladder activity in the cortex, but clinical observations on patients with bilateral lesions of the motor cortex have shown that there is commonly impairment of voluntary control of micturition (Foerster, 1936; Holmes and Sargent, 1915; Lewis, Langworthy and Dees, 1935). Graphic records of the activity of the detrusor muscle during filling in patients who had cerebral lesions associated with imperative micturition and incontinence have indicated that a hyperactive response to stretching of the muscle is present (Lewis, Langworthy and Dees, 1935; Watts and Uhle, 1935). Therefore, it is not unlikely that the continuous incontinence in our case was caused by the tumour interfering with tracts descending from those parts of the brain concerned with the voluntary control and tone of the bladder and rectum.

The paralysis of the lower limbs, which gradually progressed during

the patient's stay in hospital, was first noted at the time of admission and probably resulted from involvement of the long tracts in the midbrain by the tumour. It was impossible to be sure of the actual onset because symptoms of epidermophytosis developed several weeks before admission and masked the symptoms of paralysis. On examination in hospital the pupils were fixed, but no strabismus or defect in conjugate movement of the eyes was observed. With the aid of the red lens, paresis of the left external rectus muscle was shown to be the cause of the diplopia. It is surprising that more severe ocular palsies were not present, as the region of the oculomotor nuclei in the midbrain was markedly invaded by the tumour. The deterioration of the higher critical faculties in this patient, as shown by lack of initiative and increasing disregard for personal cleanliness and tidiness, and the associated emotional instability and withdrawing of the personality were probably the result of generalized cortical degeneration due to long-continued internal hydrocephalus. It is likely that impairment of cortical function also played a large part in the production of the masturbation which was such a striking symptom in this case. That bilateral cortical destruction involving the frontal lobes can cause deterioration in the sexual habits of the individual is shown by the case reported by Brickner (1934). In his patient, following partial bilateral frontal lobectomy, the author states that 'the formerly normal sexual activities have regressed to a masturbatory level'. The total disregard for the presence of others which was manifested by our patient during masturbation may have been entirely the result of intellectual deterioration. It is possible, however, that the performance of the act in public was an attempt to compensate for his consciousness of inferiority in sexual development. The impairment of critical faculties might have acted as the determining factor causing the mental conflict to seek gratification by the public display. To account for the extraordinary frequency of the masturbatory acts while the patient was under observation, it might be suggested that impairment of the inhibitory influence of the cortex on lower centres, mediated by the fronto-hypothalamic tracts, resulted in a release phenomenon by which the intensity and number of sensual impulses reaching consciousness were increased. The ascendancy of these impulses in consciousness might be favoured by the patient's increasing detachment from his environment. In addition, an absolute increase of *libido* may have been present due to a hormonal cause. The hyperplasia of the interstitial cells in the testes suggests that there was hypersecretion of the male sex hormone.

The symptom of insatiable appetite for more than a year is of interest in this case, particularly as it was associated with gradual loss of weight and a normal basal metabolic rate. Morbid hunger has long been noted as an occasional finding in cerebral disease. It is probably more common in frontal lobe lesions, but has been noted by Spiller (1909) in a case having a glioma of the pons. Fulton, Jacobsen, and Kennard (1932) observed that monkeys, after bilateral removal of the frontal lobes, ate several times as much as

normal animals, although the basal metabolic rate was unaltered. Fulton suggested that the symptom of morbid hunger might be due to increased motility of the stomach. He based this suggestion on the abnormal peristalsis of the gut, which has been noted following experimental extirpation of the premotor cortex on both sides. Watts (1935) brought forward the additional suggestion that a part of the excessive appetite and tendency towards emaciation might be the result of food being hurried through the alimentary canal at a rate that does not allow time for digestion and absorption to be completed. He concluded that marked hunger associated with brain tumours, cerebral vascular disease, and accidental injury to the brain is probably due to irritation or destruction of the intestinal representation in the cortex or of tracts arising there. It is reasonable to assume that the excessive appetite in this patient, which was associated with progressive loss of weight, was primarily due to interference with cerebral function as a result of the tumour.

*Gonadal features.* The clinical signs most difficult to explain are the testicular atrophy and the deficient secondary hair. According to a statement made by the patient, his testes were well developed at seventeen years of age (six years before) and they had become smaller since that time. In view of his defective memory at the time the history was obtained, too much reliance cannot be placed on the time period given. But the fact that he recognized that they had regressed in size indicates that sexual development had progressed normally up to a period well after puberty. This view is corroborated by the indisputably normal size of the penis together with capacity for erection and the frequent masturbation with emission at the time of admission to hospital. The finding of normally developed seminal vesicles, epididymis and prostate gland at autopsy is conclusive confirmatory evidence of normal maturation. In endeavouring to reconcile the presence of the above signs indicative of normal sex function with the defective secondary hair distribution and atrophied seminiferous tubules, it is necessary to recognize the chronology of the development of sex characters in the normal male. As is well known, the adult development of penis and accessory sex organs precedes by a matter of many months or years the attainment of secondary hair characteristic of the adult male. In the subject of this report, the history and findings indicate a normal sex development until the late 'teens' at least. The secondary hair seems never to have fully developed, the hypogonadism having apparently set in before this process would normally have been completed. Of all the secondary sex characters this, however, was the only one defective. The hypogonadism was, therefore, but partial and was in no sense true eunuchoidism, for in such cases atrophy of accessory sex organs ensues, as has been shown in studies of eunuchs and in experimental investigations following castration in animals (Moore, 1932).

*The gonadal lesion and its relation to sex characters.* The extremely small size of the testes, already noted, was due wholly to the atrophy of seminiferous tubules for, far from being diminished in amount, the interstitial

cells actually appeared hyperplastic. The presence of this tissue probably accounts for the intactness of the accessory sex organs, since it has been shown that a hormone obtained from the testis will, when injected into castrated animals, result in complete restoration of the atrophied accessory sex organs (Koch, 1932; Moore, 1935) and the balance of evidence favours the interstitial cells of Leydig as the source of this, the so-called male sex hormone (Moore, 1932; Lipschutz, 1924; Smith, Engle and Tyndale, 1934). While there is no evidence of deficient testicular hormone secretion in this case as judged by the histological appearance of the prostate, seminal vesicles and epididymis, tissues utilized experimentally for the detection of the male sex hormone, the clinical findings of defective secondary hair development and testicular atrophy were considered to be evidence of serious diminution of the hormonal activity of the testes. It remains to explain this disassociation in behaviour of the secondary sex characters. The typical hair distribution of the adult male is generally considered to be a secondary sex character dependent on the gonads, but the factors controlling this hair development are ill understood and probably complex (Danforth, 1925). It seems, on clinical grounds, that the adrenal cortex plays a rôle, but here, apart from the hair defect, there was no evidence of hypofunction of this gland although it and the thyroid and parathyroids were found to be below average size at autopsy. Whether a testicular hormone stands in direct relationship to the development of normal male hair or operates indirectly through, or in conjunction with, another gland, e.g. adrenal, is not known. However, experimental evidence suggests that a second hormone is secreted by the testis (Moore, 1932, 1935; Lipschutz, 1924; Lower, Engle and McCullagh, 1935) which, according to certain clinical observations, seems to originate in the tubule cells and be concerned with secondary hair distribution. Altmann (1930), in his exhaustive study of eunuchoidism, describes several cases in which the hypogonadism was only partial, i.e. though there was deficient secondary hair and absence of seminiferous elements in the testes, the interstitial cells were plentiful or hyperplastic and the accessory sex organs were normal (Cases 6, 7, 10 and 11). Conversely, Leydig's cells may be absent and the seminiferous element present with normal distribution of hair (Brack, 1923). From these two lines of evidence, it seems that tubule cells have to do with secondary hair distribution and, from this and previously quoted sources, that the interstitial cells are concerned with the integrity of accessory sex organs. Though such a concept explains the disassociation in the development of the secondary sex characters in our case, the actual cause of the tubular atrophy and interstitial cell hyperplasia remains unexplained and therefore will now be considered.

*Possible causes of the testicular lesion.* (1) General: The actual cause of the regression of the germinal epithelium in these testes, with which the deficiency of secondary hair may be related, is difficult to establish. As is well known, this element is highly sensitive to injury and shows regressive changes in a variety of circumstances (Moore, 1932; Lipschutz, 1924; Jaffe and Berberich, 1932). *In febrile states* degeneration may be marked: in pneumonia,

as described by Mills (1919), and in tuberculosis, as noted by Scylla (1928). Vitamin (A and E) deficiency, radiation, and alcohol, all lead to severe injury to the germinal tissue of testes (Moore, 1932). In this case there was no evidence to implicate the above factors and it is justifiable therefore to attempt to correlate the testicular findings with the cerebral lesion.

(2) Pineal: The view that the hypogonadism was due to a hyper- or hypo-secretion by the pineal gland or by tissue associated with the tumour receives little support from experimental or clinical studies. While we do not propose to consider in detail the pathological physiology of the pineal gland, nor to discuss exhaustively the mass of controversial literature concerning its possible endocrine nature, which has been done recently by Berblinger (1930), Benda (1932 *b*), and Calvet (1934), a brief consideration of pineal function is in order. The occasional association of tumours of this organ with the development of sexual precocity in young children was ascribed originally by Marburg (1908) to hypopinealism. However, the occurrence of *pubertas praecox* with tumour of the pineal gland is the exception rather than the rule (Berblinger, 1930; Benda, 1932 *b*; Haldeman, 1927). Most recent witnesses in this regard, Globus and Silbert (1931), found in five verified cases of pinealomata in children only one showing changes suggestive of precocious sexual development, and these were of very slight degree; while Ford and Guild (1937) were unable to find a single instance of *macrogenitosomia praecox* associated with pinealoma recorded in the literature. Pineal tumours manifesting themselves in adult life have but rarely been observed to produce any change in the sexual organs. Complete removal of a pineal gland containing a tumour in a female patient known to us (Pratt and Brooks) has not resulted in any evidence of endocrine dysfunction in the individual in the two years which have elapsed since the operation. During this time she has become pregnant and has recently been delivered of a healthy child. Similarly in the case of a male aged thirty-five, reported by Berblinger (1930), the testes were normal and showed spermatogenesis though the pineal was destroyed. There is some evidence, however, that in young children absence of the pineal gland may be associated with failure of development of gonads and secondary sex characters. Zandren (1921) reported such findings in a boy who died at the age of sixteen, and autopsy showed nothing to account for them but complete absence of the pineal gland. Zandren concludes that the function of the pineal gland is essentially of a secretory nature and is principally concerned in the initiation of puberty. Though this view is contradicted by cases such as that of Askanazy and Brack (1921), where hypoplasia of the pineal was associated with precocious puberty, it receives some support from the experimental work of Rowntree and his co-workers (1935) who found that the injection of pineal extracts into successive generations of rats caused a progressive acceleration in development of size and sexual maturity. Although evidence such as this would suggest a definite endocrine function of the pineal gland, contradictory evidence is again met in the considerable number of reports by investigators who have obtained only negative results from

pinealectomy in the rat, rabbit, dog, and chick. Certain positive results which have been reported suggest that ablation of the pineal leads to premature development of the secondary sex characters in the male, giving a clinical picture similar to *pubertas praecox* in the human being. This evidence is not conclusive, however, and is not in harmony with the findings of Rowntree, although it does receive some support from the work of Engel (1935) who has shown that in rodents the gonadotropic hormone is inhibited by the injection of suitable pineal extracts. Finally, as Ford and Guild (1937) have emphasized in their recent report, *pubertas praecox* has been recorded as occurring with encephalitis and tumours of the third ventricle not affecting the pineal gland in any way. 'While we are not immediately concerned with the problem of the place of the pineal gland in the production of *pubertas praecox*, the alleged association has been used as an argument for the endocrine nature of that organ but, owing to the inconclusiveness of the evidence both experimental and clinical, one cannot with certainty attribute any hormonal function to the pineal. Particularly is this true after puberty has occurred and, since we are not aware of any instance in which a pinealoma has been associated with regressive sexual changes, the assumption would not be justified that an excess or deficiency of pineal gland secretion caused the testicular atrophy and consequent failure in development of secondary hair in our patient.

(3) Pituitary: Pituitary lesions have long been recognized as a cause of genital disturbances, but in our case the pituitary cannot be held primarily responsible for the testicular changes since there was no evidence of any chronic degenerative process or neoplasm in the gland. Nevertheless, since research in the past decade has so clearly demonstrated the importance of the anterior lobe in the control of the genitals, the possibility must be entertained that disturbed function of this tissue occurred secondarily to the cerebral lesion. Such a hypothesis affords the most reasonable explanation of our findings and is supported by both the clinical and experimental evidence which will now be examined. Complete cessation of the function of the anterior lobe of the pituitary, whether the result of disease (Simmonds, 1914; Farquharson and Graham, 1931; Silver, 1933) or of experimental hypophysectomy (Crowe, Cushing and Homans, 1910; Smith, 1927*b*) leads to atrophy of all testicular elements and accessory sex organs. Less complete lesions involving but a small part of the glandular portion of the pituitary are encountered not infrequently, but the occurrence of a limited pituitary lesion in association with testicular changes similar to those met with in our patient is an exceedingly rare phenomenon. We are aware of only five instances recorded in the literature. Four of these cases, analogous to our own with respect to gonadal changes, are detailed briefly herewith.

Case 1, described by Uemura (1917). A man, aged 29, showed a calcified mass in the *pars nervosa* and a cyst in the intermediate lobe of the pituitary. The pineal, thyroid, and gonads were atrophic; the parathyroids, adrenals, and accessory sex organs apparently were normal. The similarity to our case lay in the microscopic finding of tubular atrophy and interstitial cell

hyperplasia in the testes and in the defective development of secondary hair. Cirrhosis of the liver was also present.

Case 2, reported by Remé (1935), was a man aged 46 in whom the gross findings were a fractured skull and contused brain, marked atrophy of testes, but normal hair distribution. This last fact does not contrast so strongly with the opposite finding in other cases when one considers the age of the patient. Evidence from other sources indicates that prevention of the development of secondary hair occurs more readily than regression. Cross section of the pituitary gland in this case showed a cyst which occupied almost the whole intermediate lobe of an otherwise normal gland. Histologically, the testes showed only a few hyalinized remnants of the seminiferous tubules, but an absolute increase of interstitial tissue. Presumably the other endocrine organs and accessory sex organs were normal as they are not mentioned. In explanation of his case the author says: 'Es bleiben daher für unseren Befund nur zwei Möglichkeiten der Deutung übrig: Entweder hat ein isolierter Ausfall der Pars intermedia eine Atrophie beider Hoden mit reaktiver Zwischenzellwucherung verursacht oder es hat die Unterbrechung der Verbindung zwischen Vorder- und Hinterlappen zu dieser Veränderung geführt. Jedenfalls wird durch unsere Beobachtung gezeigt, dass eine hypophysäre Hodenatrophie ohne wesentliche Vorderlappenschädigung und damit ohne wesentliche Störung der Abgabe der Vorderlappenhormone an das Blut durch ein Versagen der Hormonabgabe an die nervöse Substanz zustande kommen kann. Wir neigen dazu, in unserer Beobachtung einen Beweis für die morphologische Existenz und die funktionelle Sonderstellung der Pars intermedia im Sinne von Biedl, Aschoff, Cushing u. A. zu sehen.'

Remé refers to a report by Poos on a similarly situated cyst in a dog in which degeneration of the follicles of the ovary was found.

The following two cases in which compression of the pituitary by an intrasellar tumour gave a similar testicular picture are cited by Berblinger (1920).

Case 3. A man aged 24, in whom death was due to pulmonary tuberculosis, showed defective distribution of secondary hair. A tumour was found in the anterior pituitary, compressing but not destroying the intermediate lobe. There was atrophy of the tubules of the testis without interstitial cell hyperplasia.

Case 4. A man aged 40, in whom the pars intermedia was compressed by an anterior lobe tumour. The specificity of the influence of this lesion is rendered doubtful, however, by the coexistence of a glioma of the third ventricle and internal hydrocephalus. Spermatogenesis was deficient and also the connective tissue, but the interstitial cells of the testes were not hyperplastic. Berblinger interpreted the testicular change in these cases as due to blocking of the excretory path of a hormone.

These experiments of nature, in which a portion of the pituitary is anatomically or functionally deleted by disease, provide evidence for the existence of two gonad-stimulating factors in the pituitary, a concept wholly in harmony with experimental facts comprehensively reviewed recently by Collip (1935), Evans (1935), and Smith (1935). While female animals have been used almost exclusively until recently in the investigation of gonadotropic hormones, convincing demonstration of the individual control of the two testicular elements by separate hormonal fractions has been reported. Smith, Engle and Tyndale (1934) showed that extracts of follicle-stimulating hormone from

menopause or castrate urine, when injected into hypophysectomized male rats, produce profound response in seminiferous epithelium with slight or no response of the interstitial tissue, as shown by histological studies, and failure of accessory reproductive organs to hypertrophy. The same response was obtained by Evans, Pencharz and Simpson (1934) from a principle obtained by fractionating the hypophysis, which indicates that the follicle-stimulating hormone obtained from urine is of pituitary origin. Contrasting with this effect is the result obtained from injection of other gonadotropic preparations whether they be from pregnancy urine, pituitary, placenta, or pregnant mare's serum. These preparations affect the chief internal secreting component of the testes—Leydig's cells. Thus the pituitary gonadotropic hormones, commonly designated 'follicle-stimulating' and 'luteinizing' from their action in the female, apparently have their effects in the male on the seminiferous epithelium and interstitial tissue respectively. Additional evidence in support of this concept has been provided by Greep (1937), but in a recent report Evans, Simpson and Pencharz (1937) claim to have shown that luteinizing and interstitial cell stimulating effects of pituitary extracts are due to separate entities. Though the identity of the gonadotropic hormone stimulating Leydig's cells must therefore be considered *sub judice*, the luteinizing and the interstitial cell stimulating factors, if not one, are so closely associated that they may, for practical purposes, be considered as one substance. So, in the remainder of this paper, the terms luteinizing and interstitial cell stimulating hormone will be used as synonyms. In the light of the above concept of the gonadotropic hormones, the atrophy of the seminiferous tubules in our case and in the four analogous cases cited can be logically explained by postulating a deficiency of the 'follicle-stimulating' or, to use the generic term, the gametogenic hormone of the pituitary. That the pars intermedia is intimately concerned in the secretion or excretion of that hormone is suggested by the site of the pituitary lesion in the cases reported by Uemura, Remé and Berblinger. Such a simple statement does not, however, explain the selective nature of the pituitary defect, Remé's explanation notwithstanding. It is difficult to understand how the hormonal function of the pituitary could have been affected so that failure of but one gonadotropic factor resulted and an examination of clinical and experimental work bearing on the problem does not provide adequate explanation for these cases. It does, however, contribute to an understanding of pituitary function in general and the control of the secretion of gonadotropic hormones in particular, thereby providing a concept of the mechanism of the changes in our case. Final interpretation of many pituitary lesions will become possible, we believe, only when scientific disclosures amplify the incompleteness of our knowledge and bring order to the chaotic mass of information on the subject. In view of our belief that this happy era is not far distant, a somewhat detailed consideration of this literature is probably justified.

*Influences Causing Failure of Secretion of the Gametogenic Hormone*

It is generally considered that the gonad stimulating substances originate in the anterior lobe of the pituitary, together with thyrotropic, adrenotropic and other fractions. That the secretory function of this tissue was not defective in respect of the interstitial cell stimulating hormone in our case, or in any of the four cited cases, is shown by the normal or hyperplastic state of the interstitial cells in the testes. Evidence of failure of hormonal activities of the anterior lobe, other than seminiferous tubule atrophy, is noted only in one instance, the atrophic thyroid in Uemura's case. The problem, then, is to explain how the secretion of the gametogenic hormone may fail while the luteinizing and other hormonal functions of the anterior pituitary apparently remain normal. To do this it is necessary to postulate (a) that there is a high susceptibility of the hormone or its secretory mechanism to injury, or (b) that the gametogenic or seminiferous tubule stimulating hormone may have an origin, a path of excretion or a mechanism of extraneous control differing from the other hormones. In one of those ways it would be sensitive to influences which either do not seriously affect or do not act on the other hormones of the anterior pituitary.

(a) The high sensitivity to injury of the secreting mechanism of the pituitary with regard to its gonadotropic hormone or hormones can be inferred from the well known fact that sexual dysfunction may precede by a matter of months or years other signs of pituitary disease. In Berblinger's cases quoted (Cases 3 and 4), the gross structural defect caused in each case by an intrasellar tumour could have caused hormonal disturbance by reduction in the amount of secreting tissue or by interference with the circulation to that tissue. Cases 1 and 2 cited may possibly be explicable on the latter basis too. In any event, the various lesions in the four cases apparently affected but one hormonal function of the pituitary, namely that governing the growth and maintenance of the testicular tubules. This would suggest that the effective margin of secreted gametogenic hormone must be very narrow and that various influences readily reduce this below the threshold level for tubule response. An alternative, though less plausible, hypothesis would suggest this hormone may itself be more sensitive to various influences than others, e.g. oxygen lack, toxins, &c.

(b) The lesion in Uemura's case, and in Remé's case also, particularly suggests that the intermediate lobe may actually be the site of origin of the gametogenic hormone. Such a hypothesis has the merit of simplicity and would at once explain how it was possible for disease to produce such a selective failure in pituitary function without grossly affecting anterior pituitary activities. Acceptance of this explanation is hazardous, however, the fundamental difficulty residing in the inconclusiveness of the evidence for the existence of an intermediate lobe in the human as a functional entity. Certain authorities, notably Aschoff (1930) and Biedl (1930), after reviewing the facts in some detail, conclude in favour of the independent existence of

an intermediate lobe. Cushing (1932, 1934) appears to be of this opinion also. Others, however, including Kraus (1926), Benda (1932*a*), Berblinger (1932) and Rasmussen (1937) hold the opposite view. Consequently, interpretation of the singular type of testicular atrophy in these cases on the basis of obliteration of the function of the intermediate lobe rests on a somewhat insecure foundation. While certain of the authorities referred to above doubt the morphological independence of the pars intermedia, it is a widely held belief that this tissue does secrete into the pars nervosa a substance which is, or becomes, the posterior lobe hormones, and that this substance is excreted *via* the stalk into the third ventricle. Recent work has cast doubt on the validity of this view, but it seems that the pars nervosa itself elaborates the pressor, antidiuretic, and oxytocic hormones. Fisher (1937), who has reviewed the matter in detail, has also shown that the morphologically normal pars intermedia present in cats with degeneration of the posterior lobe following lesions interrupting the supraoptico-hypophyseal tracts is also functionally normal, as judged by its melanophore-expanding activity on the live frog. While this work constitutes evidence in favour of the independent existence of the pars intermedia in the cat, it does not shed any light on the possibility of a gonadotropic hormone being secreted there. However, the fact that certain species, such as the chicken and the whale, have no pars intermedia, indicates that the hormonal function of this tissue may be taken over by the anterior lobe. Thus de Lawder, Tarr and Geiling (1934) found the melanophore principle present in the anterior lobe of the chicken, and Geiling (1935) obtained the same result in the whale. In man the intermediate lobe, on morphological grounds alone, might be termed rudimentary. That this is true also of its function is suggested by the finding of the melanophore hormone in the anterior lobe of man by Roth (1932) and Jores and Glogner (1933). Consequently, although the gametogenic hormone might conceivably arise in the intermediate lobe in some forms, it seems certain that in the chicken and whale, and probably in man, it has its origin from the anterior lobe tissue. Therefore it is unlikely that Uemura's and Remé's cases can be explained as due to destruction of the tissue that produces the gametogenic hormone, and it may be concluded that the gametogenic hormone probably arises in the anterior lobe. The origin of the luteinizing hormone in that tissue seems certain from all available evidence, including that from the above two cases. If both gonadotropic hormones originate from the same lobe, then it is extremely unlikely that they would have different excretory paths, and it is generally agreed that the anterior lobe hormones escape from the gland by a vascular route, probably the general circulation (Wislocki and King, 1936).

Only one circumstance would render likely the excretion of the gametogenic hormone in a manner different from the anterior lobe hormones, namely a separate origin. From the immediately preceding discussion this would appear to be a very remote possibility, but, as a hypothesis most attractive, since it lends itself to a ready interpretation of some pituitary changes in

which little intrinsic pituitary damage exists. With slight variations, blocking of the excretory path of a hormone or hormones from the intermediate lobe as they pass up the stalk to the neighbourhood of the third ventricle has long been a thriving theory. More than twenty years ago Biedl (1916) suggested it as the causal mechanism of the changes in dystrophia adiposogenitalis. Since his concisely stated concept bears on this problem, his words are worth quoting:

‘Auf Grund der vorliegenden experimentellen Ergebnisse sind wir berechtigt, die Dystrophia adiposogenitalis nicht nur als Hypopituitarismus im allgemeinen aufzufassen, sondern können diese Erkrankung des näheren als Folge einer Einschränkung der Sekretabgabe von Seite der Pars intermedia betrachten. Diese kann durch direkte destruktive Prozesse, durch Kompression des Hypophysenstiemes und endlich bei intrakraniellen Drucksteigerungen des Hypophysenstiemes durch eine Verhinderung des Sekretabflusses infolge von Liquorstauung hervorgerufen sein.’

The unlikelihood of excretion of anterior lobe hormones by the stalk is further supported by the work of Squier and Wertheimer (1929) who failed to detect gonad stimulating substances in the cerebrospinal fluid of bitches. To summarize, the evidence cited concerning the pars intermedia shows it to be unlikely that this part of the pituitary gives rise to the gametogenic hormone in man. If this is so, neither obliteration of that lobe nor blocking of a hypothetical path of excretion by the stalk offers a probable explanation for failure in the secretion of the gametogenic hormone. Finally, although Berblinger suggests blocking of the path in explanation of his two cases cited, such a view does not seem valid for another case reported by him (1921). The pituitary lesion consisted of a single miliary tubercle in the posterior lobe. Profound atrophy of seminiferous tubules, hyperplasia of Leydig's cells, a small penis and defective development of secondary hair were the other outstanding findings in a twenty-six year old man. Though the pulmonary tuberculosis from which the patient died might be blamed for the degeneration of the seminiferous epithelium, the co-existence of the unusual testicular picture and pituitary lesion is sufficiently rare an occurrence to merit mention here. Unfortunately no data are given concerning the actual position or size of the tubercle. The obvious way in which the lesion could have affected the hormonal activities of the adenohypophysis is by the interruption of the nerve fibres which, running down the stalk, are known to pass through the pars nervosa and into the intermediate lobe (Greving, 1926; Pines, 1926). According to Hair (1937) the fibres also penetrate into the anterior lobe in the cat.

As previously suggested, work during the last fifteen or twenty years shows that the pituitary and hypothalamus have a close functional relationship, constituting in many respects a functional unit. Roussy and Mosinger (1933) and Collin (1933) have recently discussed these relationships at length. With regard to sex function, with which we are concerned, it has been shown that experimentally produced lesions of the hypothalamus result in genital atrophy, as reported by Aschner (1912), Camus and Roussy (1926), Bailey

and Bremner (1921), Houssay and Hug (1923), Smith (1927*b*) and others. Clinically too there are numerous instances of genital dystrophy occurring when damage to the diencephalon exists, but the number of cases in which a histological description of the gonadal lesion appears is lamentably small. The suggestion that the sex effect of such brain lesions is mediated through the pituitary was mentioned by Biedl (1916) in the extract quoted above. This comment is particularly interesting here in its recognition of extra-pituitary lesions as a cause of hypophyseal symptoms. Gottlieb's (1921) suggestion that damage to Edinger's tract would also give rise to the picture of dystrophia adiposogenitalis implies a mechanism by which a more purely extrasellar cerebral lesion may affect pituitary function. Probably the effect of internal hydrocephalus on the pituitary is not due to blocking of the passage of secretions up the stalk, as Biedl suggested, but to interference with the hypophyseal nerve or vascular supply. Though vascular disturbances may be responsible for pituitary changes in those cases in which gonadal dysfunction is the only evidence of hypophyseal aberration, the anterior lobe would appear to be less susceptible to such injury than the posterior lobe, in virtue of the disposition of its blood vessels (Wislocki and King, 1936). Impairment of blood supply sufficient to affect the function of the anterior lobe would, we suggest, be more apt to produce multiple signs of pituitary deficiency than the sole defect evident in our case.

An infundibular centre regulating genital function is postulated in a recent publication of Cahane and Cahane (1934) in which many instances of genital dystrophy are cited. It should be pointed out that in many of the cases referred to by these authors, complete loss of sex function occurred, which was not found in our patient. This may be but a matter of degree of involvement of the hypothalamus, and some factor other than a deficiency of gonadal hormones must be operative in such cases, for it is a well established fact that normal sexual relations may be continued many years following post pubertal castration (Moore, 1932). In the absence of extensive regression of pituitary function, it appears unlikely that testicular atrophy resulting from damage to the nerve connexions of the hypophysis is sufficient to produce impotence. For this disturbance in the physiological act of erection, injury to other tracts or important centres of the autonomic system in the diencephalon is probably necessary. In cases, such as ours, having extrasellar cerebral lesions, injury to nerve fibres supplying the pituitary gland seems a more likely explanation for the highly selective nature of the changes in the gonads than any of the previous possibilities considered. The probable mechanism of disturbance in the nerve supply of the hypophysis will now be examined.

#### *Neuro-humoral Regulation of Gonadotropic Hormone Secretion*

Recognition of the fact that the hypothalamus has an important part in the regulation of sex function is of great value, though simplification of the

problem by postulating a centre for such purpose is liable to hinder rather than help in the solution of what is undoubtedly a complex mechanism. Evidence illustrating the dynamic role of the nervous system in relation to hormonal activity of the hypophysis has recently been disclosed by experimental physiologists. The approach to this problem was facilitated by the singular fact that the rabbit ovulates only after coitus. This phenomenon was utilized by Fee and Parkes (1929) who first demonstrated that the cause of ovulation in the rabbit is secretion of a hormone by the pituitary in response to the stimulus of copulation. They found that inhibition of ovulation occurred when hypophysectomy was performed within, but not later than, one hour and a half after mating. Later investigations of Friedgood and Cannon (1936) showed that the chief path by which the nervous stimulus affects this hormonal secretion is not the sympathetic; while the work of Marshall and Verney (1935) suggested that the central nervous connexion of the pituitary is the important route. Brooks (1937) has conclusively demonstrated this to be the case in rabbits, since, with the hypophyseal stalk severed, ovulation did not occur though the animals mated frequently. Ablation of both cervical sympathetic chains did not appear to impair ovulation. Cellular changes in the anterior hypophysis following coitus in the rabbit have recently been described by Friedgood and Dawson (1937). These changes are characterized by the appearance of a hitherto unrecognized granular cell staining selectively with azocarmine. It is presumably associated with the elaboration of the luteinizing hormone which initiates the act of ovulation and corpus luteum formation. That it is the luteinizing hormone which is secreted under these circumstances is shown by the experiments of Schweizer, Charriper and Haterius (1937) who found that transplantation of the pituitary to the anterior chamber of the eye of the hypophysectomized female guinea pig produced a state of continuous oestrus with the formation of many follicles, but neither actual ovulation nor corpus luteum formation occurred. This work is of great importance since it demonstrates that the cyclical nature of sex function is controlled by the periodic release of the luteinizing hormone from the pituitary, and that for this the nervous connexions of the gland are necessary. In the absence of its nerve supply, the pituitary appears to elaborate the gametogenic, but little or none of the luteinizing hormone. This indicates that in the intact animal either the luteinizing hormone or the neurogenic factor causing its secretion has the ability to suppress the secretion of the gametogenic hormone. Though it seems most probable that the secretion of both gonadotropic fractions is of cyclical nature, it is possible also that the gametogenic hormone is normally secreted at a constant rate, and some only of its effects are inhibited by the periodic activity of the luteinizing hormone. That protracted secretion of the luteinizing hormone is associated with suppression of a fundamental function of the gametogenic hormone, ovulation, is well attested to by several biological phenomena of which pregnancy is the most outstanding example, but it is not possible to say whether this is due to

diminished gametogenic hormone secretion or to excess of the luteinizing factor, or to both. The product of the luteinizing hormone activity, the corpus luteum, is particularly important in lower animals, but even in them, following the initial nervous stimulus to corpus luteum formation, the products of conception actuate the continuance of secretion of the luteinizing hormone. The latter process is probably even more important in higher forms in which the nervous discharge of the luteinizing hormone after copulation is thought to be an unimportant feature. Nevertheless, it seems reasonable to suppose that the sex cycle is regulated by a periodic discharge of nerve impulses to the anterior pituitary, though the control of this may in turn be related to the sensitizing influence of the level of oestrin or to some other hormone in the blood acting on hypothalamic centres. The second phenomenon illustrating the suppressing influence of the luteinizing hormone on follicle stimulating hormone activity is seen in pseudo-pregnancy produced in rodents by allowing the female to copulate with a vasectomized male. The dioestrous interval which ensues as a result of the corpus luteum formation demonstrates clearly the hypersecretion of the luteinizing hormone brought about by the sexual stimulus which is transmitted to the pituitary by nerve fibres. The effector nerve path by which the luteinizing hormone secretion is stimulated, as previously noted, is not by the sympathetic fibres which reach the gland by way of the carotid vessels. It seems probable, then, that the nerve fibres important in this respect are parasympathetic representatives reaching the gland by the stalk, not necessarily by the supraoptico-hypophyseal system, but possibly from parasympathetic centres in the tuber. There may also be some descending parasympathetic fibres which join the sympathetic system in the neck. For the above reasons, and on teleological grounds, the chemical mediator of the nerve discharge leading to secretion of the luteinizing hormone would appear to be acetylcholine. It is interesting to note in this connexion that excitement is followed at times by the early onset of menstruation in some highly strung females. This phenomenon may be interpreted as due to the death of the corpus luteum resulting from the cessation of secretion of the luteinizing hormone, consequent upon the sympathetic stimulation or parasympathetic inhibition, or both. Therefore it is logical to conclude that the hypothalamus and the nerve fibres which it gives to the anterior pituitary constitute an important controlling link in the secretion of gonadotropic hormones, that secretion of the luteinizing hormone is accompanied by a suppression in the formation or effects of the gametogenic hormone, and that acetylcholine is probably the chemical mediator of parasympathetic nerve impulses regulating this process.

#### *Interpretation*

In our patient, and in most of the clinical cases cited, the testicular lesion is explicable by postulating a reduction in the secretion of the gametogenic hormone, but not of the luteinizing factor. In only one of these instances

does there seem a likelihood that the great sensitivity of the tubule cells to non-specific injury could have been a factor. This was in the third of Berblinger's cases, where the existence of tuberculosis may be suspected of producing the injury. In his other two cases, the rather gross lesion in the anterior lobe may, by its mechanical effect, have caused a reduction in the gametogenic hormone to such an extent that degenerative changes in the seminiferous epithelium ensued. Though a similar reduction in luteinizing hormone may have occurred also, the injury threshold at which degenerative effects become apparent was obviously not reached. Uemura's and Remé's cases may be interpreted in a similar fashion since it is possible that mechanical or vascular changes occurred as a result of the lesion in the pars intermedia. This location of the lesion, on the other hand, may have interfered with the parasympathetic innervation of the anterior lobe, but such a view we cannot co-ordinate with the explanation arrived at for our case in which such injury seems improbable. It is unlikely that gross interference with the nerve supply by the stalk occurred in our case, in view of the absence of both polyuria and degeneration of the posterior lobe, which Ranson and his co-workers (Fisher, Ingram and Ranson, 1935; Fisher, Ingram, Hare and Ranson, 1935; Ingram, Fisher and Ranson, 1936; Fisher and Ingram, 1936), have shown to be sequelae of damage to the supraoptico-hypophyseal tract in the cat and monkey. Though experiments of Mahoney and Sheehan (1936) have cast doubt on such an occurrence following severance of these tracts at the stalk in the monkey, the report of Biggart (1936) supports Ranson's observations. The thesis we submit in explanation of our case rests on the factual and theoretical basis expounded above. It is suggested that the testicular picture observed could be produced by prolonged preponderance of parasympathetic impulses acting on the anterior lobe of the pituitary. This in turn would lead to discharge of a quantity of luteinizing hormone constantly in excess of the gametogenic hormone, whose secretion would be concurrently reduced. Only one of two circumstances could lead to this occurrence, either an irritative stimulus affecting a parasympathetic centre or tract related to the pituitary, or a relative preponderance of the parasympathetic due to withdrawal of the influence of the sympathetic. This second alternative we believe to be the case, and we consider that there are two ways in which this could be brought about: firstly, by compression or destruction of the descending sympathetic tracts in the midbrain by tumour tissue; or, secondly, by damage to the diencephalic sympathetic centres from either the tremendous distortion of the third ventricle or invasion of the hypothalamus by tumour tissue as found at autopsy. In support of this hypothesis we suggest that the morbid hunger observed was also a result of parasympathetic preponderance due to suppression of sympathetic activity. In explanation of the actual hyperplasia of interstitial cells, it is not necessary to postulate hypersecretion of the luteinizing hormone, for the observation of Lipschutz (1924) indicates that conditions causing a break-down of seminiferous elements induce an increase in the cells of Leydig. Experimental confirmation of this view is found in

the results of Smith, Engle and Tyndale (1934) who observed that the interstitial cell response was greater when pregnancy urine extract only was injected into hypophysectomized rats than when both testicular elements were stimulated by simultaneous injection of castrate and pregnancy urine. The pregnancy urine injection, according to the theory enunciated, would parallel the conditions obtaining in our case. Finally, more specific explanation is afforded by the concept of Lower, Engle and McCullagh (1935). These authors submit evidence for the secretion of a hormone by the seminiferous tubules, termed 'inhibin'. This hormone, they say, holds in check the luteinizing pituitary gonadotropic factor. Absence of the tubules results in excessive secretion of the luteinizing hormone by the pituitary, according to the observations of these investigators. However, in a recent communication McCullagh (1937) has virtually retracted this belief.

#### *Summary*

1. A case of pinealoma in a man aged twenty-three, with invasion of the brain stem and hypothalamic region and associated internal hydrocephalus, is reported.

2. The significance of the various signs and symptoms is discussed in some detail. The earliest symptom was somnolence, which appeared about four years prior to death and gradually increased in severity. Changes in intellect and personality were outstanding manifestations, but symptoms indicating involvement of the cranial nerves and the tracts in the midbrain were surprisingly few in view of the extensive invasion of this region found at post-mortem examination.

3. The most unusual findings on examination were testicular atrophy and defective development of secondary hair. The history suggests that the gonads regressed in size some time after the age of seventeen and that the hair distribution of the normal adult male had never developed fully.

4. The testes on histological examination showed complete atrophy of the seminiferous tubules and hyperplasia of interstitial cells. The penis and the accessory sex organs appeared normal macroscopically. The prostate, seminal vesicles, and epididymes were examined microscopically and presented a normal appearance. These findings show that there was no defect in the secretion of the male sex hormone, a product of the interstitial tissue.

5. No evidence of chronic disease was found on examination of the pituitary gland. The pars intermedia tissue was scanty in amount, but a consideration of the literature throws considerable doubt on the importance of this lobe in the human hypophysis and indicates that wide variations in amount are common without any associated disturbance. Therefore, there is not sufficient evidence to hold the pituitary gland primarily responsible for the testicular findings in this case. The adrenal, thyroid, and parathyroid glands were all below the average in size, but showed no marked histological abnormality and no definite clinical evidence of dysfunction.

6. The maldevelopment of the secondary hair in this patient is attributed,

at least in part, to the absence of the seminiferous tubules and of a hormone, other than the male sex hormone, which they secrete.

7. The possible causes of the testicular atrophy are discussed. No evidence was found in the literature which indicated that either hyper- or hypofunction of the pineal tissue could produce such an effect, nor were there substantial grounds for considering avitaminosis or toxic influences responsible.

8. After a consideration of the experimental and clinical evidence available, it is concluded that the unusual type of hypogonadism resulted from a disturbance in the nerve supply to the pituitary gland. It is suggested that the pineal tumour, directly or indirectly, caused destruction of sympathetic tracts in the midbrain or of sympathetic centres in the hypothalamic region. Reasons are given for believing that the consequent preponderance of the parasympathetic influence on the gland led to a discharge of an amount of luteinizing hormone relatively in excess of the secretion of the gametogenic gonadotropic fraction which was concurrently suppressed. An associated depression in the secretion of adrenotropic and thyrotropic factors is a further possibility and suggests a cause for the small size of the adrenals and thyroid. Hypofunction of either of these glands might conceivably have contributed to the defective hair growth.

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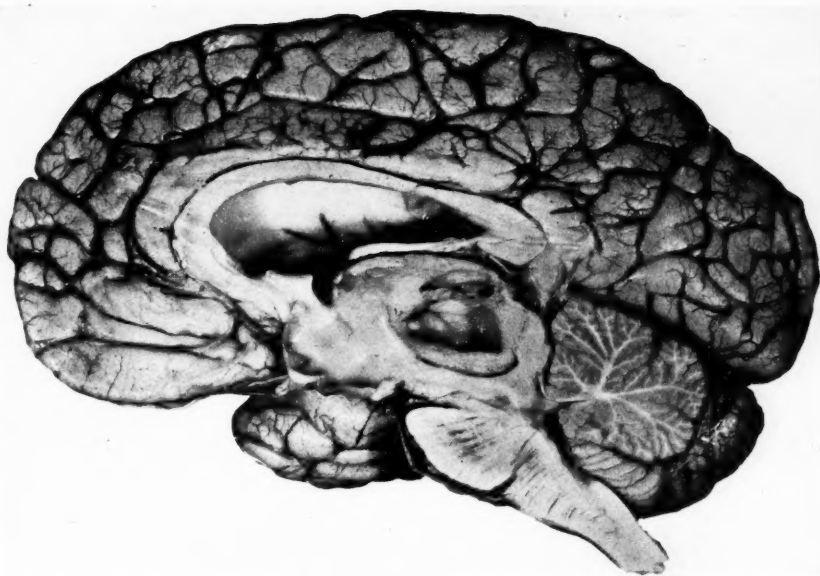


FIG. 1. The mesial surface of the right half of the brain, demonstrating a large tumour arising from pineal parenchyma, infiltrating and destroying the tissue of the midbrain. The tumour has compressed the superior and inferior colliculi backward. It has undergone cystic degeneration, the cystic spaces being filled with clear yellow fluid. Compression of the aqueduct has caused severe distension of the third and the lateral ventricles. The flattened optic chiasma is seen in the anterior part of the floor of the distended third ventricle. The tumour is greyish-white in colour with ill-defined boundaries

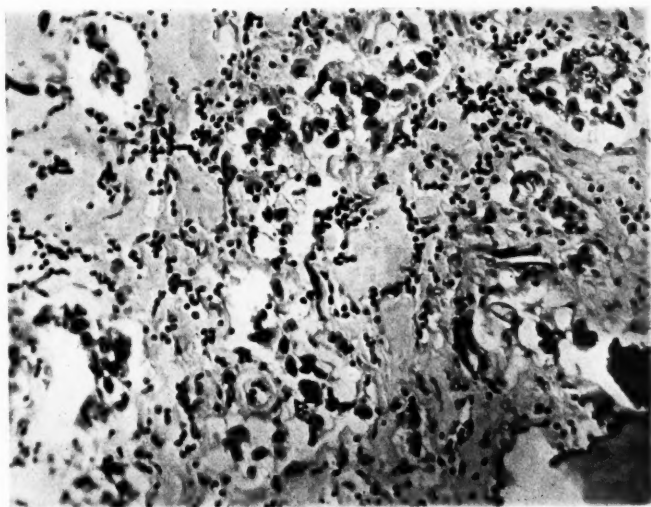


FIG. 2. Low power photomicrograph ( $\times 100$ ), stained with haematoxylin and eosin. This shows the large and the small cellular elements of the tumour, the larger cells showing a definite tendency to alveolar formation. There is considerable hyaline degeneration of the tumour tissue visible in this photograph, and to the extreme right a mass of calcium can be seen



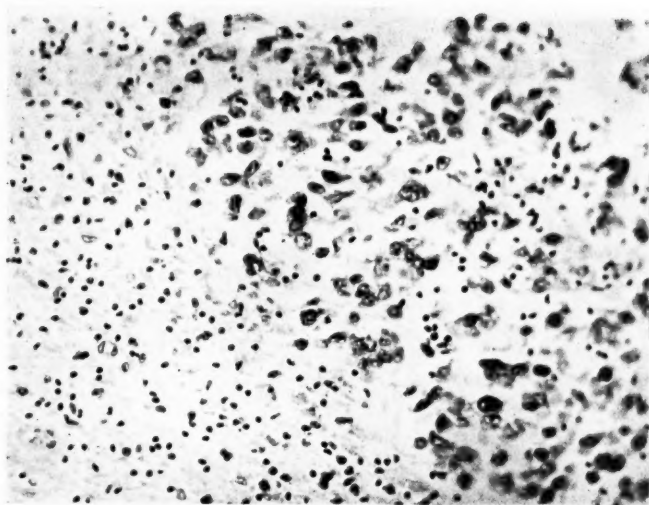


FIG. 3. A low power photomicrograph showing invasion of mid-brain tissue by the pineal tumour cells

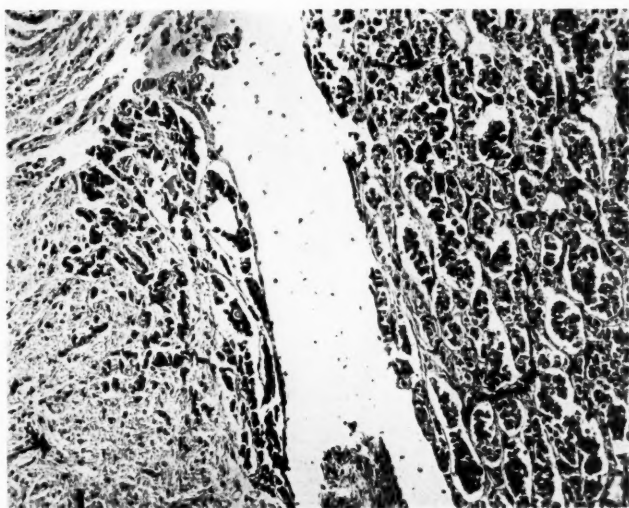


FIG. 4. Low power photomicrograph of the pituitary gland showing anterior lobe, pars intermedia and posterior lobe tissue. The gland was uniformly congested and red-blood corpuscles can be seen in the space separating the anterior lobe and pars intermedia tissue



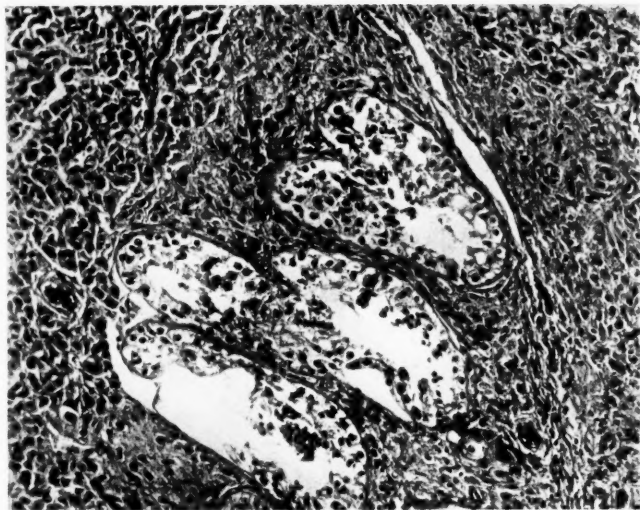


FIG. 5. Low power photomicrograph of testis showing atrophic tubules lined by degenerate Sertoli cells. To the left of the photograph large numbers of Leydig cells are seen

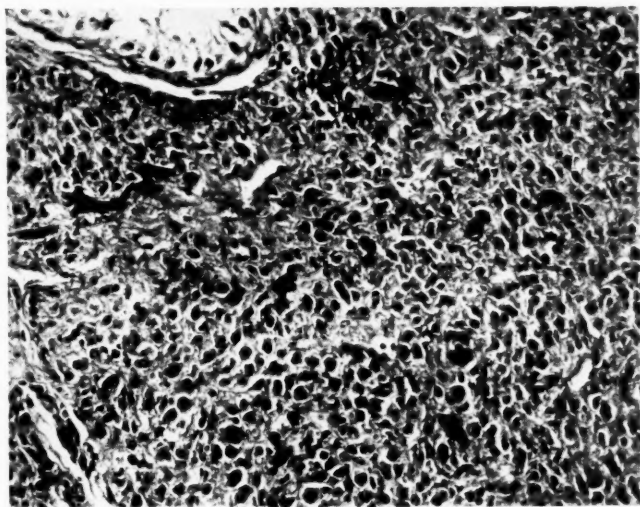


FIG. 6. Higher magnification of testis to show Leydig cells which made up the bulk of the tissue of the testis





FIG. 7. Tubules of epididymis from the region of the rete testis, lined by normal high columnar, ciliated epithelium. Spermatozoa were not found in their lumina

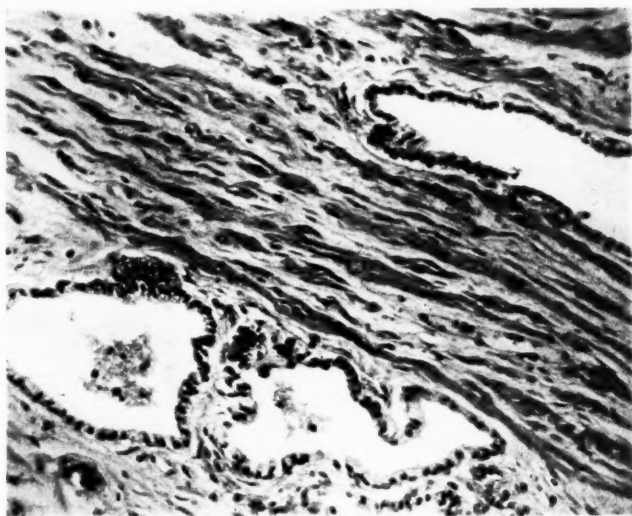
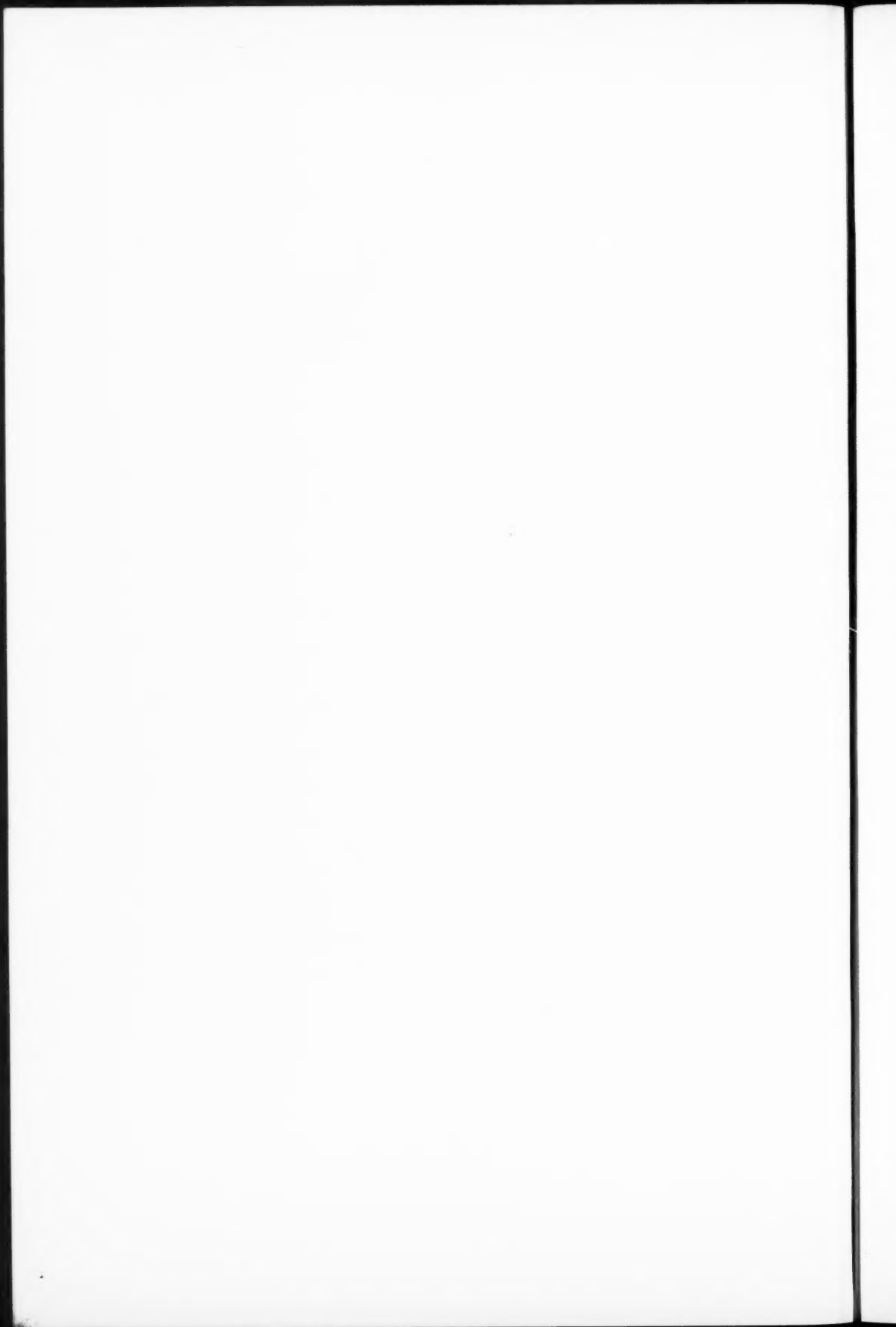


FIG. 8. Low power photomicrograph of prostate gland, showing a normal histological structure



MYELOMATOSIS<sup>1</sup>

By ALICE STEWART IN COLLABORATION WITH F. PARKES WEBER

(From the Royal Free Hospital)

With Plates 16 to 18

*Introduction.* The present paper, which contains a full report of four cases of myelomatosis, is chiefly concerned with an inquiry into the presence or absence of changes in the blood proteins and serum calcium, and the association of the disease with amyloidosis. Several reports of hyper-proteinaemia in myelomatosis have recently been published and are of interest in view of the well-known association of this disease with Bence-Jones' protein in the urine, but it is not clear how often this change occurs or upon what it is dependent. Although the present investigation has failed to throw much light on these difficulties, it is hoped that the report of our findings may ultimately be of value. A rise in the serum calcium and an excessive excretion of the mineral, similar to that found in parathyroid tumour, has also been observed in this disease and is now recognized as being very common. This is of importance, as not infrequently cases of myelomatosis are subjected to the unnecessary operation of parathyroidectomy, often with fatal results. A careful analysis shows that even in this respect differences exist which may be sufficient to determine the diagnosis. This is clearly shown in the present series. The coexistence of amyloidosis with myelomatosis has been especially stressed by Magnus-Levy (1933), and recently Atkinson (1937) has collected 40 cases from the literature. In only one of the present series was any amyloidosis discovered, but this case showed so many remarkable features and the amyloid material was deposited in such an unusual way that we have reported it in detail. For a complete review of the literature of myelomatosis the reader is referred to Atkinson's paper, which contains a full list of references to all the published cases.

1. *Changes in the blood proteins, and associated phenomena.* In 1848 Bence-Jones published his classical observations on 'a new substance occurring in the urine of a patient with "mollities ossium"'. The case was reported two years later by Macintyre (1850) and, though at that time regarded as one of osteomalacia, is now clearly seen to be one of multiple myeloma. The frequent association of this disease with an unusual type of protein in the urine—subsequently given the name Bence-Jones' protein—was soon

<sup>1</sup> Received December 3, 1937.

recognized, but it is not until 1899 that one finds any reference to changes in the blood proteins. During that year Ellinger, in a paper on the diagnostic significance of Bence-Jones' proteinuria in bone tumours, records a case in which there was in the blood-serum an abnormal protein which was precipitated on heating to 56° C. He also comments on the tendency to rouleau formation in the blood of this patient. In 1911 Hopkins and Savory noted that it was impossible to do a blood count on one of their patients with myelomata owing to the clumping of the red cells; but the next direct reference to the subject does not occur until 1917 when Jacobson reported a case which he described as 'Multiple Myeloma with chronic nephritis showing Bence-Jones' protein in the urine and blood serum'. He noticed that during the inactivation of the blood in the performance of the Wassermann reaction, the serum being heated to 60° C. for 30 minutes, a heavy creamy-white precipitate appeared. This substance alone represented 7.86 gm. per cent., but, unfortunately, no figure is given for the total protein, though this was believed to be 'very high'. The urine contained 1 per cent. of albumin and Bence-Jones' protein was present. In 1925 Pribram published a case in which, in spite of an unusual degree of polycythaemia and the absence of direct post-mortem or biopsy evidence, was almost certainly one of myelomata. The value for the total plasma proteins was found to be 8.7 gm. per cent. This is the first definite report of hyperproteinaemia in the disease, but in three cases previous to this one the serum proteins were investigated and all gave values of less than 7 gm. per cent. In 1933 Magnus-Levy collected 31 published cases with reports on the blood proteins, eighteen of which gave values over 8 gm. per cent. In addition he reported five cases of his own, three of which gave values of over 9 gm. per cent. and two between 6 and 8 gm. per cent. By 1937 Atkinson had found 60 cases with total proteins ranging from 8.7 to 18.4 gm. per cent. Not included in these are two cases of Peters and Eisenmann (1933) mentioned in a paper on 'Serum proteins in diseases not primarily renal or cardiovascular' as having hyperproteinaemia. They give no values, but record that the globulin is increased at the expense of the albumin. Gutman, Swenson and Parsons in 1934 also mention that the hypercalcaemia which they have found in three cases of myelomata 'is usually associated with an increase in the protein'. A case published by Salveson under the title of 'hyperproteinaemia in a case of nephrosis without oedema' is of special interest in view of the possibility that it was really one of myelomatosis. The patient, who was a man aged 60, had had a febrile illness four months previously which had been followed by weakness and persistent albuminuria. There had been no oedema, headache, or cardiac symptoms and the blood-pressure was only 88/55. The urine contained 1.6 gm. per cent. protein, with occasional hyaline and granular casts, and the specific gravity ranged from 1.001 to 1.023. There was no blood or pus in the urine, the water excretion was good and there was no retention of urea. Subsequently the proteinuria was found to vary between 0.5 and

2.2 gm. per cent., 20 to 56 per cent. of which was estimated as 'globulin'. The blood proteins showed a total value of from 8.97 to 10.73 gm. per cent. with 1.69 to 2.56 per cent. albumin, 7.10 to 8.32 globulin, and 0.52 fibrinogen. The non-protein nitrogen varied from 25 to 36 mg. per cent. and the serum calcium (one estimation) was 9.6 mg. per cent. The patient was not seen again by Salveson, but he apparently remained in fairly good health for eight months, with no oedema in spite of persistent albuminuria. He then developed pneumonia and died. Unfortunately there was no necropsy or X-ray examination so the case cannot be proved, but the absence of pain is not incompatible with the suggested diagnosis, as several cases have recently been published in which pain was absent throughout the illness. This was also a feature of one of our cases (Case 2) over the two years during which he was watched. In practically all cases of myelomata with hyperproteinaemia, the increase in the protein has been due to the globulin fraction, the albumin often being very low, whilst the fibrinogen has been either slightly or conspicuously raised. In one case (Reimann, 1928) a rise of the fibrinogen to the record value of 5.48 gm. per cent. represented more than half the total protein. As a rule there is a gross alteration in the albumin-globulin ratio, a fact which has been regarded as the probable cause of many of the associated phenomena observed in the blood. Normally this ratio approximates to 2.2; in myelomatosis values of 0.5 are not uncommon. In addition to reports on hyperproteinaemia there exist many published cases of myelomata in which the blood proteins show normal or low values. In these cases there is no alteration in the albumin-globulin ratio, but several of them show abnormal serum precipitates, usually on heating to between 50° and 60° C., which are also found in many of the cases with raised blood-proteins. No conclusions can be drawn as to the percentage incidence of hyperproteinaemia owing to the absence of systematic investigations on this point, nor does there appear to be any clear correspondence between the blood proteins and the presence or absence of Bence-Jones' protein in the urine, as this may or may not be present in either group. The finding of abnormal coagulations in the blood has led to various attempts to demonstrate the Bence-Jones' protein in the serum. In spite, however, of many claims to the contrary, no conclusive proof of its presence has been made. The most suggestive case is that reported by Cantarow (1935) who found on heating the serum to between 50° and 60° C. that a precipitate formed which became less dense on further heating to 85° C., reappeared on cooling again to 65° C., and finally disappeared at 10° C. In no other case has the clouding of the serum been found to diminish on further heating, though in the two cases of Shirer, Duncan and Haden (1932) the precipitate after thorough washing was redissolved in boiling water. Magnus-Levy believes that the substance is really a highly unstable form of euglobulin and has produced experimental evidence to prove that this substance causes a heavy coagulum on heating to 56° C. Wintrobe and Buell (1933) also call attention to the fact that

the temperature of precipitation and solution of a protein are not constant and may be influenced by many factors such as the concentration of the protein, the hydrogen-ion concentration, and the total quantity of electrolytes or urea present. In their case of myelomatosis, in a sample of citrated blood, a layer of dense yellowish material appeared in the plasma immediately above the blood corpuscles at room temperature. This was examined microscopically and found to consist of viscid masses of varying size. After standing on ice, the plasma showed throughout a further cloudy white precipitate which disappeared at room temperature, but reappeared on further cooling. In Karlins and Lundquist's case (1933) a fine milky-white precipitate formed above the layer of red cells when trichloroacetic acid was added to the blood. In addition to such findings the following points have been noticed in connexion with alterations of the plasma proteins in myelomatosis:

(a) *Failure of clot retraction.* On leaving a sample of such blood to stand, a coagulum forms which is much firmer and whiter than normal. Even after a long period there is no retraction of this clot and frequently it has been impossible to obtain more than a drop or two of serum without forcible compression. This appearance is recognizable *post mortem* when the blood-clots in the heart and larger arteries appear stiff and fill the vessels, quite unlike the retracted clots normally seen.

(b) *The tendency to exaggerated rouleau formation in blood smears.* Normally there is a certain tendency to aggregation of the red cells in dried films, but the rouleaux in healthy blood do not contain many corpuscles, are irregular in form, and show no great tendency to join together. When exaggerated, however, the rouleaux contain very many more corpuscles, which are more closely and regularly united with one another and the rouleaux themselves are clustered to an extremely high degree.

(c) *Autohaemagglutination.* This is a change similar to rouleau formation occurring in wet films and represents a rapid spontaneous agglutination of the red cells in their own serum. This action of the serum on its own blood corpuscles may make it extremely difficult to recognize a compatible donor, as the profound haemagglutination that occurs is distinguished from true isoagglutination of incompatible blood cells only if the patient's serum is diluted.

(d) *Clumping with Hayem's solution.* Occasionally on mixing the blood in a pipette with Hayem's solution considerable granule formation results which prevents a count being made. No such effect is found if normal saline is used.

(e) *The sedimentation rate.* In every case with raised blood proteins in which this test has been done the sinking velocity of the blood corpuscles has been found to be enormously increased. In one of Foord's (1935) cases it was as much as sixteen times as rapid as in a control case with a similar blood count.

(f) *Abnormal viscosity of the blood.* Values for blood viscosity have been

recorded in only three cases of myelomatosis with hyperproteinaemia, but in each the value was very high. Thus in one of Magnus-Levy's cases, measured at 36° C., the whole blood viscosity was 7.0, whilst in Reimann's (1932) and Veil's cases it was 7.0 and 4.1 respectively. Wintrobe and Buell (1933) give no exact figure but note that the viscosity was 'extremely high'.

(g) *Spontaneous thrombosis.* This occurred in the case observed by Wintrobe and Buell which has already been mentioned as showing a serum coagulation at room temperature. In this case, which was originally thought to be one of Raynaud's disease, in addition to a curious mottling of the arms and legs with blueness of the extremities, which occurred in spite of normal warmth and pulsation in the limbs, there were frequent bruises and extensive changes in both fundi which were diagnosed as a bilateral thrombosis of the central retinal veins, changes which were believed to have been due to capillary obstruction. In only two other cases have there been reports of thromboses occurring in myelomatosis; in neither was there any record of the blood proteins. Wallgren's (1920) case had tumours in the skull associated with thrombosis of the intracranial sinuses, and Venturi's (1901) had similar findings, together with thrombosis of one central retinal artery. In one of Foord's (1935) cases, on compressing the eyeball until the circulation just ceased in the arteries and the venous flow became sluggish, large red granules were seen slowly following one another along the course of the veins. This did not occur in the eye of the author on similar pressure.

In a paper on 'The Suspension Stability of Blood' Fåhræus offers the clue to some of the above observations. He found a complete parallelism between rouleau formation and sedimentation rate. Both depend on changes in the plasma, being increased by concentration and decreased by dilution, and both are especially affected by the addition of hydrophil colloids, to which class the plasma proteins belong. He also showed that, in addition to augmenting the agglutination tendency of the erythrocytes, an increase in globulin and fibrinogen caused an increase in the aggregation tendency of the thrombocytes. Further, he made observations on the effects of compression of the eyeball on the circulation in the retinal vessels. Normally it was found that the arterial flow had to be stopped for several seconds before there appeared fine granulations in the vascular bed, but, in cases with greatly increased sedimentation rates, aggregates of erythrocytes appeared on slight pressure. In one case of pneumonia a granulated bloodstream was seen in the retinal vessels without any artificial decrease in the velocity of flow. Fåhræus concludes from his work that rouleau formation and sedimentation velocity are due to changes in the interspace between the blood cells and the plasma, either by reduction of the relative electric charge or by deprivation of the surface colloids of water. Such a change is brought about by alterations in the albumin-globulin ratio, and where there is accumulation of the globulin and fibrinogen, an increase in the plasma

viscosity also results. It is of interest to note that hyperproteinaemia in one case of myelomata may be associated with a different set of phenomena from that found in another. Wintrobe and Buell's case is apparently unique, and, whilst in four of Foord's patients there was autohaemagglutination and exaggerated rouleau formation, in only two was there any clumping of the red cells in Hayem's solution. Nitrogen retention in the blood frequently occurs in this disease, in spite of there being no increase in the blood-pressure or any other evidence of chronic nephritis. It is possible that this is in part connected with the changes in the plasma proteins. Bell (1933), in a paper on 'The Renal Lesions in Myeloma', after excluding some cases of renal failure due to concomitant arteriosclerosis, which is common during the age period in which myelomatosis most frequently occurs, and others due to the accidental association of an enlarged prostate or caused by a pyelonephritis resulting from compression of the spinal cord by a myeloma, concludes that the only direct effect of the disease on the kidney is the formation of casts of Bence-Jones' protein, which obstruct the tubules and cause tubular atrophy. When large numbers are blocked extensive atrophy of the cortex with renal insufficiency ensues. He found no evidence to support the old theory of the toxic action of the Bence-Jones' protein on the tubules and glomeruli. In one instance (Foord and Randall's case No. 1 (1935)) the renal insufficiency was apparently caused by the accumulation of a highly concentrated protein solution in the glomerular capillaries, whilst in two others a similar appearance was found in a few capillaries. As all three cases of Foord's showed hyperproteinaemia and a great increase in the blood-urea, he suggests that 'possibly changes in the osmotic pressure in the glomerular vessels may in part explain the nitrogen retention, since the tendency for the blood with an increased osmotic pressure due to the increased proteins is to hold electrolytes and absorb water from the tissues'. As the hyperproteinaemia is usually associated with a low blood-pressure there is probably a decreased output in the glomeruli and consequently a diminution of excretion of nitrogen bodies. The possibility of one other factor playing a part in the urea retention is suggested by us. Namely, that there is a constant break-down of nucleo-proteins derived from the tumour cells which increases the load on the kidney. That this break-down is occurring is suggested by the values given for the blood uric acid in the cases in which this has been reported. Twelve such cases have been collected (Table I) in which the values range from 4.5 to 31.1 mg. per cent. Undoubtedly the retention of uric acid is influenced by any associated renal insufficiency, but many of the values are too high to be accounted for in this way.

2. *Alterations in calcium metabolism.* Whilst evidence of metastatic calcification in myelomatosis was observed as early as 1907 and has been frequently confirmed since, the first record of a raised serum calcium that has been traced by us occurs in a case described by Charlton in 1927. In this patient the serum calcium varied from 12.06 to 16.0 mg. per cent., there was

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extensive rarefaction of all the bones, and metastatic calcification was seen *post mortem* in the kidney tubules. A year later Belden (1928) published a case of uncertain diagnosis with extreme hypercalcaemia. The patient was a woman complaining of loss of weight, weakness, pain and tenderness on pressure under the right breast, and pain in the lumbar region radiating down the thigh. On examination she was found to have a moderate anaemia,

TABLE I

*Values for Blood Uric Acid collected from Cases in the Literature*

Date.	Reference.	Sex.	Age.	Blood urea. mg. %	Non-protein nitrogen. mg. %	Blood uric acid. mg. %	Plasma Protein. gm. %
1928	Perlzweig et alia *	Male	40	—	34	31.1	12.3-13.8
1929	Bannick and Greene	Male	43	66	—	5.2	6.5- 7.3
		Male	64	50	74	4.5	6.0
		Male	56	50	—	5.7	—
1929	Short and Crawford	Male	52	—	35.4	5.2	—
1932	Shirer et alia	Male	64	45-210	—	4.8	10.1-13.8
1935	Cantarow	Female	41	—	93	6.1-13.6	8.7-11.3
1935	Foord and Randall	Male	57	—	148	20.0	18.4
		Male	56	—	40.6	7.0	12.7
1935	Foord	Male	44	—	33	4.3-10.0	13.2-10.1
		Male	68	—	160	12.0	15.0
		Male	52	—	200	10.0	—

\* Full report of case given by :—Geschickter, C. F., and Copeland, M. M., *Arch. Surg.*, 1928, xvi. 807.

slight albuminuria, but no Bence-Jones' proteinuria, and a normal blood-pressure. Radiograms of the lower dorsal and lumbar spine, the ribs, and pelvis showed 'marked osteoporosis with a mottled lacy appearance suggesting great absorption of lime salts'. The blood calcium was found to vary from 15.3 to 18.7 mg. per cent. with an inorganic phosphorus of 3.7 mg. per cent. A diagnosis of hyperparathyroidism was made, but operation failed to reveal any parathyroid abnormality. The patient died in a few days and no necropsy was allowed. In all probability this was a case of myelomatosis, as the X-rays showed changes consistent with this disease and the blood-phosphorus value was noticeably higher than that usually found in generalized osteitis fibrosa. Since then several cases of myelomata have been published in which there have been high calcium values in the circulating blood, and some of them were originally mistaken for hyperparathyroidism. In all, however, instead of there being a low inorganic phosphorus, such as occurs in cases of generalized osteitis fibrosa (except in the very terminal stages when the kidney failure is extreme), the phosphorus was either normal or raised, values of 6.8 and 8.0 mg. per cent. being recorded in exceptional cases. This finding has been confirmed in the present investigation and appears to constitute a valuable diagnostic distinction between these two diseases. Although comparatively few records of calcium balance exist, the earliest being that of Blatherwick in 1916, all show that where hypercalcaemia is present in myelomatosis the excretion is greatly in excess of the intake. Hunter (1935)

has recently recorded a valuable series to confirm this point and further shows that in cases in which the circulating calcium is normal there is no increase in the excretion. With one very doubtful exception, no evidence of excessive parathyroid activity has been observed in connexion with these changes in calcium metabolism, though glands removed at operation and *post mortem* have been repeatedly studied. The one exception, which has been quoted by Hunter, is a case published by Barr and Bulger (1930) in which three parathyroid glands were found *post mortem* of slightly larger size than usual, the largest measuring  $1.1 \times 0.5$  cm. Microscopic examination, however, failed to reveal any evidence of hyperactivity of the cells and it is probable that the glands were in all respects within normal limits.

3. *Amyloidosis with myelomatosis.* Apart from the classical cases of amyloidosis due to recognized causes such as prolonged suppuration, tuberculous caries, advanced gummatous syphilis, and late Hodgkin's disease, there is a group of cases in which some substance allied to amyloid material is systematically deposited in various tissues and organs of the body, notably in a nodular or tumour-like way, with a preponderance in certain parts. Such cases have been classified under the heading 'systematized atypical amyloidosis' and must be distinguished from those of isolated so-called 'amyloid tumours' in the tongue, nose, conjunctivae, &c., which have occasionally been reported. Of cases of 'systematized atypical amyloidosis' some of the most remarkable are those associated with 'amyloid macroglossia,' the Lubarsch-Pick syndrome (Weber, Cade, Stott and Pulvertaft, 1937), but amyloid deposits are also found in myelomatosis, notably cases in which Bence-Jones' proteinuria is a feature. This association has been especially studied by Magnus-Levy. Whether the amyloid substance in all these syndromes is identical appears doubtful, for the metachromatic staining reactions are not always the same. It appears, however, probable that in the cases of myelomatosis with amyloidosis the infiltrating amyloid substance is formed owing to a pathological change in the protein metabolism, connected in some way with the myelomatous permeation of the bone marrow, just as it is extremely likely that the Bence-Jones' proteinuria reflects some such metabolic change. This does not necessarily imply that in the typical cases of amyloidosis associated with prolonged suppuration, especially bone caries, the substance is produced by a toxic action on the bone marrow due to the products of suppuration. It seems to us more probable in such cases that the amyloid substance is a product of the decay of the diseased tissues. In certain rare cases of atypical amyloidosis, unstriped and striped muscle cells of involved parts appear themselves to have undergone an amyloid change, but it is impossible to prove that the process is not really one of infiltration of the fibres.

*Cases*

Four cases are reported, three plasmacytomas showing Bence-Jones' protein in the urine and one lymphocytoma which had no Bence-Jones' proteinuria. Only Case 1 out of the four showed hyperproteinaemia, and there was no abnormal serum coagulation, but one of the patients with low blood proteins (Case 4) showed clouding of the serum on heating to 56°C. The observed hyperproteinaemia persisted until death and was accompanied by failure of clot retraction, autohaemagglutination, and excessive rouleau formation. All the cases showed hypercalcaemia, values ranging from 10.3 to 19.5 mg. per cent., and this was constantly associated with a value of more than 3.2 mg. per cent. for the blood inorganic phosphorus, in contrast with the low phosphorus values usually found in generalized osteitis fibrosa. One of the cases (No. 3) had a persistent macrocytic anaemia and in one (No. 2) the blood count was within normal limits. The other two patients showed a low colour-index anaemia, and in none was the white cell count raised. With the exception of a few myelocytes and myeloblasts in the terminal stages of the case with the macrocytic anaemia, there were no abnormal white cells found in the circulation. A high blood-urea associated with a normal blood-pressure was a feature of all the cases so examined except one (Case 2) in which the blood-urea was normal. Also the blood uric acid, estimated in three of the cases, gave values of over 4 mg. per cent. Case 4 showed tumour-like amyloidosis of remarkable distribution, and in one of the two patients examined *post mortem* metastatic calcium was seen in the kidney tubules. The data from the chemical and other investigations in the four cases have been collected together in Table II.

*Case 1.* R. S. Male aged 50 years. Admitted to the Royal Free Hospital on July 7, 1936, complaining of pain in the right leg of three months' duration with increasing weakness, pallor and loss of weight. For three weeks there had been bleeding from the mouth. On examination there was marked pallor with some recent loss of weight, and stomatitis with bleeding from the lips, tongue and gums. Tenderness on pressure over the right hip was present. There was no oedema and no enlargement of liver, spleen or lymph glands. The blood-pressure was 140/80. The urine contained albumin and the X-rays showed extensive irregular rarefaction of the pelvic bones which suggested the possibility of generalized osteitis fibrosa. The patient discharged himself before further investigations could be made, but was readmitted on August 13 as the pain in the leg had become increasingly severe. There was then no longer any bleeding from the mouth, but there was slight oedema of both ankles. A sample of blood was taken for calcium estimation, and this showed such remarkable properties that the plasma proteins were examined and the true nature of the disease realized. Hitherto no tests for Bence-Jones' protein in the urine had been made, but this was then shown to be present in considerable amounts. The blood showed a remarkably high total protein with great increase in both the globulin and fibrinogen and a very low albumin. The sinking velocity of the red cells was enormously increased and there was almost spontaneous clotting of the supernatant plasma which

set into a stiff jelly, and even after two weeks showed no retraction of the clot. No precipitate appeared on heating the serum to 60° C. or on saturating either with sodium chloride in an acid solution or with magnesium sulphate. The blood calcium and phosphorus were raised and also the plasma viscosity. A blood count showed a severe anaemia, but though there was no abnormality in the total or differential white-cell count, the films showed a remarkable

TABLE II  
Data Tabulated from the Investigation of the

Case.	Date.	Total plasma protein gm. %	Albumin.	Globulin.	Fibrinogen.	Hb. %	R.B.C.'s millions per c.mm.	W.B.C.'s per c.mm.	E.S.R. min. per hr.	Viscosity of blood.	Viscosity of serum
1. Male, aged 52	14.8.36	12.3	1.34	9.96	1.1	34	2.37	8,000	—	8.0	4.3
	28.8.36	12.2	1.5	9.8	1.1	24	1.42	7,750	82	—	—
2. Male, aged 51	11.11.36	5.27	4.21	1.06	0.78	—	—	—	17.5	4.4	1.6
	1.12.36	4.65	3.60	1.05	0.17	85	4.27	5,200	1.5	—	—
3. Female, aged 21	18.12.36	7.1	4.65	2.45	0.84	45	1.77	6,400	75	—	—
	30.12.36	6.35	4.1	2.27	0.35	—	—	—	—	—	—
	June 37	6.3	5.1	1.2	—	17	0.71	9,000	—	—	—
4. Male, aged 36	10. 3.36	—	—	—	—	51	2.50	6,200	—	—	—
	14.12.36	7.3	5.2	2.1	0.32	45	1.90	6,800	67	—	—
	16. 6.37	7.25	4.41	2.84	0.2	45	1.95	10,000	—	—	—

tendency for the red cells to run together. In attempting to find a suitable donor, great difficulty was at first experienced as there was apparent clumping of all four groups. Finally, it was realized that with the compatible donor (Group A) this was autohaemagglutination and not true isagglutination. On diluting the patient's serum the true difference became apparent. The blood-urea was greatly raised and the urea concentration test gave a maximum value of 2 per cent. urea in the urine after ingestion of 15 gm. of urea. The following calcium balance experiment was performed:—the patient and a control subject in the same ward were kept on a weighed diet of known low calcium content, the total intake of calcium being approximately 100 mg. a day. All the stools and the total urine output for each twenty-four hour period were collected and a daily creatinine estimation was done on the latter to check the completeness of the specimens. The experimental period was divided into two by three doses of carmine and the output of calcium in urine and faeces during the second three days was estimated. The findings showed a great increase in both the urinary and faecal output of calcium in the patient with myelomatosis. The value for the urinary calcium during the three-day period being 885 mg. as compared with the control value of 335 mg. (an excess of 550 mg.), whilst the faecal calcium for the same time was 1126 mg. as compared with 661 mg. in the control (an excess of 465 mg.). During the patient's three weeks in hospital the pain spread across the lower part of the back and affected both hips. There was also tenderness and

limitation of movement over the lower lumbar vertebrae. The oedema of the ankles became more marked and two days before death there was abdominal distension, but no vomiting. On Sept. 4 the temperature rose to 101° F., the patient failed rapidly and died in coma next day.

*Necropsy.* The vertebral column, the lower six ribs on the left side, the sternum, the right femur and humerus and the whole of the pelvis and skull

II  
of the Cases Described

Viscosity of serum	Serum calcium mg. %	Inorganic phosphorus mg. %	Blood urea mg. %	Blood uric acid mg. %	Blood pressure mm. Hg	Urine albumin.	Urine B. J.	Remarks.
4.3	19.5	3.5	146	—	140/80	+	+	Plasmacytoma (P.M.). Blood also showed: excessive rouleau formation, failure of clot retraction, autohaemagglutination. No abnormal serum precipitates. Negative calcium balance.
—	15.5	3.3	82	—	140/80	+	+	
1.6	10.7	3.83	—	—	135/80	tr	+	Initial records taken immediately after a pathological fracture. Plasmacytoma (Biopsy).
—	—	—	35	4.4	—	nil	nil	
—	12.7	3.8	52	4.6	110/45	tr	nil	Macrocytic anaemia with myelocytes in the circulation. Lymphocytoma (P.M.). Yellowish pigmentation of skin. Metastatic calcification in kidneys (P.M.).
—	13.9	3.8	70	—	132/75	tr	nil	
—	13.1	4.3	93	—	—	tr	nil	Negative calcium balance. Serum precipitate on heating to 56° C. Extremely little erosion of cortex of bones. Generalized amyloidosis. Plasmacytoma (marrow puncture).
—	10.3	4.5	39	—	—	++	++	
—	13.2	5.4	69	5.7	124/78	++	++	
—	13.9	5.0	94	6.9	—	++	++	

showed numerous grey-white and maroon-coloured fleshy tumours varying from a few millimetres to several centimetres in diameter. In some of the bones the growth had caused distension of the marrow cavity with partial destruction of the overlying corticalis which was often so thin as to be readily cut with a knife. The right ilium was conspicuously expanded and here the tumour had eroded right through the bone and extended into the ilio-psoas muscle and sacrum. In addition, both suprarenals contained several soft greyish-white nodules of growth and there were several small, hard black nodules the size of a pin's head on the pleural surface of both lungs. One tiny nodule was present beneath the capsule of the liver and another in the cortex of the right kidney. The lymph glands and spleen were not enlarged. The heart and aorta were filled with stiff gelatin-like clots and the myocardium showed well-marked fatty degeneration. There was no enlargement of the thyroid or parathyroid glands, and the brain and reproductive organs appeared normal. Histological examination of the tumours in the bones, kidney, liver and suprarenals showed in all parts a similar microscopic picture which consisted of masses of rounded cells, the majority resembling the typical plasma cell. The arrangement of these cells was diffuse with a scanty connective tissue stroma separating the different groups. Amongst the typical plasma cells were scattered some with more deeply staining, smaller nuclei, and occasional mitotic figures could be seen. In some of the tumour nodules, especially those in the suprarenals, they were occasional giant-cell forms with

two or three nuclei. In the bone marrow at the edges of the tumour masses, plasma cells and marrow cells were intermingled and there was evidence of considerable haemopoietic activity in the unaffected areas. Haemorrhage and necrosis were present in the larger growths. The nodules from the lung were found to consist of fibrous tissue surrounded by several microscopic collections of tumour cells. There was no histological evidence of growth in the spleen, liver, or lymph glands and the parathyroid tissue appeared in all respects normal. The kidneys showed albuminous casts in the tubules and coagulated serum in the glomerular capillaries and within some of Bowman's capsules. There was no amyloid degeneration and no evidence of metastatic calcification in any of the organs examined. For laboratory tests see also Table II.

*Summary.* The case showed a very considerable degree of hyperproteinaemia associated with marked hypercalcaemia. The former was caused largely by increase in the globulin fraction of the protein with some increase in fibrinogen and was accompanied by failure of clot retraction, rouleau formation of the red cells, autohaemagglutination, and increased viscosity and sedimentation rates. The rise in serum calcium was accompanied by a negative calcium balance and a high value for the plasma inorganic phosphorus, but there was no post-mortem evidence of metastatic calcification. Typical renal insufficiency with great nitrogen retention, albuminuria, Bence-Jones' proteinuria, and casts in the urine was found associated with a normal blood-pressure and no arteriosclerotic changes. The tumour cells conformed to the typical plasma cell type and metastases appeared in the suprarenals and lungs without there being any invasion of the extramedullary haemopoietic tissues.

*Case 2.* E. R. Male aged 50 years. In March, 1935, the patient noticed a sudden cracking sensation in his right arm whilst swinging a pail of water. The pain and swelling in the upper part of the arm which followed brought him to hospital. Examination revealed a fracture across the upper part of the right humerus and a radiogram showed 'an irregular rarefaction of the upper third of the bone with a pathological fracture (?) due to a secondary carcinomatous deposit'. Careful search, however, failed to reveal any primary growth and the patient appeared in good health with no evidence of anaemia or wasting, and no pain. While the fracture was being treated a swelling appeared over the lower end of the sternum. On X-ray examination this was seen to be due to expansion of the bone, which contained several irregular areas and gave a general 'mouse-eaten' appearance. All the remaining bones in the skeleton were then X-rayed, but with negative results. The urine was examined and found to contain Bence-Jones' protein, and a biopsy on the affected humerus showed a typical plasma-cell myeloma. No further examinations were made at this time. The fracture in the humerus healed satisfactorily, and after a course of deep X-ray therapy the areas of rarefaction in the two affected bones became appreciably smaller. The patient returned to work and remained in perfectly good health with no pain until November 1936 when he fell and injured the right arm again. All the bones were X-rayed again on this occasion, but the disease appeared to be confined to the humerus and sternum as before. The urine still contained Bence-Jones' protein and some albumin, but there was no retention of urea or non-protein nitrogen, no increase in the plasma proteins and no clouding of the serum on heating to 60° C., nor were there any associated changes such as autohaemagglutination or abnormal clot formation and the sedimentation rate was not increased. The haemoglobin was 85 per cent. and the white-cell count was normal in all

respects. There was, however, a slight rise in the blood-calcium and inorganic phosphorus. Details of laboratory tests are included in Table II.

*Summary.* A case in which the disease appeared to have remained localized to two bones for at least twenty months and to have caused little or no constitutional disturbance and no pain. There was no anaemia, no alteration of the plasma proteins and the sedimentation rate was normal. The urine contained Bence-Jones' protein and albumin and a biopsy of the affected humerus showed typical plasma cells. Both the serum calcium and the inorganic phosphorus were slightly raised.

*Case 3.* I. S. Female aged 22 years. In October, 1936, the patient attended the out-patient department of the South London Hospital for Women, complaining of fainting attacks and loss of strength for the previous three months. These symptoms had been steadily increasing in severity and for six weeks the patient had also noticed pains in the chest and shoulders and a dull ache over the lower part of the back. She appeared severely anaemic and ill and was admitted immediately.

*Examination:* Marked pallor with blue sclerotics and very slight lemon-yellow colouring of the skin. General nutrition good. Temperature 100.6° F., pulse 96, respirations 20. Heart slightly dilated, with muffled action. The blood-pressure was 110/45. There was tenderness over the lower ribs on both sides and over the lower part of the spine. Tenderness was also present along the course of the right sciatic nerve. Rectal examination revealed extreme coccygodynia. The urine showed a small amount of albumin, but no Bence-Jones' protein. There were a few hyaline casts. X-rays were taken of all the bones and these showed generalized rarefaction. This was most marked in the right lower ribs and these bones were wider than normal. Only in the skull were the punched out areas typical of myelomatosis to be seen.

*Investigations:* The blood count showed a macrocytic anaemia with a few circulating myelocytes and immature red cells, but otherwise the films were normal. There was no increase in the total protein and the albumin-globulin ratio was unaltered. The serum calcium was examined on three occasions and there was a steady rise of this and the inorganic phosphorus. The blood-urea was also slightly raised. There were no abnormal serum precipitates. A marrow puncture yielded some semi-solid, haemorrhagic material, which was found to contain very few cells. These had large nuclei and a clear cytoplasm and closely resembled lymphoblasts. In spite of being very ill the patient insisted on discharging herself after one month in hospital and was not heard of again till three months later, when she was admitted to King's College Hospital. Whilst there she was extremely ill and in great pain. She persistently refused all blood tests and investigations and discharged herself within a few weeks. In May, 1937, the patient was admitted to St. Thomas' Hospital under the care of Professor de Wesselow. She was by this time extremely emaciated and almost all the bones were tender on pressure. The skin was curiously dry and showed a uniform, light brownish pigmentation, though there was no yellowness of the conjunctivae and the mucous membranes were almost colourless. The haemoglobin on admission was 17 per cent., but subsequently fell to 11 per cent. There was bleeding of the lips and gums on admission, but this ceased later. In addition to extensive X-ray changes in the skull there were then typical punched out areas in the ends of all the long bones and in the pelvis. The urine still contained some albumin, but there was no Bence-Jones' protein by the ordinary heating test. The white-cell count was not increased, but there were several primitive

cells of the myeloid series and the anaemia was still macrocytic. The plasma proteins were still within normal limits, but the calcium and phosphorus were both raised. The patient died on June 30.

*Necropsy.* Extreme wasting, generalized yellowish pigmentation of skin. Bruising of right arm below the deltoid. A few petechial haemorrhages under the pleura and pericardium. Liver fawn-coloured with pale yellowish mottling. Both kidneys almost white. Of the bones examined the skull showed several small purplish areas which cut easily with a knife, whilst the shaft of the femur, the sternum and ribs were full of haemopoietic tissue with some form of growth. On microscopic examination this growth was seen to consist of round nucleated cells indistinguishable from those of lymphatic leukaemia or lymphosarcoma. The kidney and liver were also found to be invaded by these cells and the former contained a few metastatic calcium deposits.

*Summary.* A case occurring in a woman aged 22 years in which there was extensive erosion of the whole skeleton by tumour-like masses of cells morphologically indistinguishable from lymphoblasts, with no corresponding change in the circulating white cells. A steadily progressive macrocytic anaemia with profound emaciation and pigmentation of the skin, but no changes in the blood proteins; no Bence-Jones' protein in the urine and no nitrogen retention. Examination of the calcium and inorganic phosphorus in the blood gave persistently raised values and *post mortem* metastatic calcification was found in the kidneys.

*Case 4.* S. S. Male Polish Jew aged 35. In June, 1935, the patient attended the Royal National Orthopaedic Hospital complaining of pain in the right hip and loss of weight. Radiograms of the hip joint showed no abnormality and the condition improved on being treated with diathermy and massage. Two months later he had an acute attack of 'gout' affecting the left big toe. He also developed pain in the left hip and knee, and Bence-Jones' protein was discovered in the urine. He was admitted to St. Bartholomew's Hospital in October and given a course of deep X-ray therapy. He was discharged in December, but a recurrence of pain in both groins, both knees, and the left shoulder brought him to the London Hospital in March 1936. At this time there was pallor of the mucous membranes with aphthous stomatitis and pyorrhoea. Both hips showed great limitation of movement, but there was complete absence of any tenderness over the spine, ribs or other bones. The head of the first left metatarsal was swollen, and movement was limited and painful. No enlargement of the liver or spleen was noted. The urine contained albumin and Bence-Jones' protein in large amounts. The blood-calcium and phosphorus were both raised and there was a negative calcium balance over two three-day periods. The blood-urea was of high normal value, but the urea clearance test showed only 48 per cent. of normal efficiency. Radiograms taken on March 23 showed a slightly granular appearance of the upper ends of both femora with similar slighter changes in the left tibia and fibula. The right and left arm and hand were normal and the skull showed no changes. The left lower margin of the second lumbar vertebral body was possibly a little more translucent than is usual, but otherwise the vertebral column appeared normal. The left metatarso-phalangeal joint showed changes on the outer side suggestive of a gouty arthritis. The sternum and ribs appeared normal. Immediately after discharge from hospital the patient developed a transient swelling of the lips and tongue which was accompanied by great pain, and thereafter until his admission to the Royal Free Hospital in December 1936 there was increasing pain and stiffness in the right arm and gradual limitation

of movement in both hands with swelling of all the small joints. Since October pain had developed in the ribs and back, which prevented his walking more than 50 yards. On admission (Dec. 11 1936) he was very pale and thin. Both hands gave the appearance of typical severe rheumatoid arthritis and there was also evidence of old arthritis in the left big toe. A lump was palpable on his back attached to the 7th and 8th ribs, a smaller one also being felt just below the angle of the scapula. There was limitation of all movements in both arms at the shoulder, elbow, and wrist and in the joints of both legs, which were held fixed with the knees slightly flexed. Several hard lumps were palpable over the inner side of the right tibia. The blood-pressure was 116/80. X-rays were taken of all the bones and showed a slight irregular rarefaction in the lower end of the radius and ulna and in the carpus of both arms. There was generalized rarefaction of all bones of the feet and osteoarthritis of the left metatarso-phalangeal joint. Slight indefinite changes were also visible in the scapula and humerus of both sides, but there was nothing definitely abnormal in the ribs, pelvis or skull. A blood count showed considerable anaemia, but no abnormal white cells. The blood-urea and uric acid were raised by this time, whilst the calcium and inorganic phosphorus were still higher than in March. There was no rise in the total protein and no abnormal clot formation or clumping, but the serum clouded on heating to 60° C. and the sedimentation rate was raised. A marrow puncture was performed on January 3 and the film showed an increased number of plasma cells, which gave the Unna-Pappenheim staining reaction. The patient stayed in hospital five weeks, during which time his condition remained stationary, though there was an increase in the blood-urea, blood-calcium, and inorganic phosphorus. After discharge, although bedridden, he became much freer from pain. He attended as an out-patient for further blood tests on February 20, when the swellings were seen for the first time on both hands. He was seen again on June 14. There had been further loss of weight and two large lumps, the size of grape fruit, were seen attached to the ribs just below the angle of the scapula. There was another on the right shoulder, the skull was covered with numerous smaller nodules, and the swellings over the wrists and ankles were more prominent than before. The patient refused to come in for further investigations, but on July 30 was admitted to the Westminster Hospital under Mr. Stanford Cade. In addition to the extraordinary lumps about the joints and skull there were nodules of various sizes in the sheaths of the abdominal muscles. There was still abundant Bence-Jones' protein in the urine, also ordinary albumin and a few hyaline casts. Joint movements were still more limited than previously and the patient could not even open his mouth widely. There was emaciation and anaemia. X-ray examination showed localized distension of the medullary canal of some of the long bones and a rather irregular decalcification of most of the skeleton. On August 11 a subperiosteal nodule from near the crest of the ileum was removed, and examined by Dr. Pulvertaft. A haematoxylin and eosin section across the centre of the nodule showed an almost entirely degenerate tissue, the surviving areas of which consisted mainly of large giant cells. These were often arranged at the periphery of circular structures of the size of colloid vesicles of the thyroid, which gave a positive stain for the amyloid substance with methyl-violet, iodine and Congo red. On August 25, Congo red was injected intravenously and an hour later some tissue from the anterior part of the sheath of the left rectus muscle removed. The structure was similar to that of the specimen removed on the 11th, but the giant cells were less prominent. The amyloid material appeared to be deposited in the dense fibrous tissue of

the rectus sheath. There was no evidence of absorption of the Congo red, although 49 per cent. of the dye had left the blood-stream at the end of the hour (normally less than 30 per cent. should disappear in this time). Dr. Pulvertaft also injected rabbits intravenously with repeated doses of 5 c.c. of the patient's urine, but up to date the animals have suffered no ill effects. The Bence-Jones' protein, when precipitated by heat, was also found not to take up methyl-violet, Congo red or iodine. Further examination of the blood at this time showed no rise in the total protein and no alteration in the albumin-globulin ratio. Blood transfusion produced a temporary improvement in the anaemia, but the patient then lost ground again and in September he was removed to a home of rest. He died on October 30 and no post-mortem examination was allowed.

*Summary.* This case is remarkable for the extreme limitation of movement at all the joints; for the relatively slight erosion of the cortex of the bones, and for the complete absence of the typical punched-out areas in the X-ray photographs. In addition, the patient developed extensive amyloidosis of unique type, extraordinary lumps and thickenings appearing about the joints, backs of hands, back of thorax, calvarium, pelvis and in the abdominal wall. They were parosteal, being connected with the periosteum, bursae, tendon sheaths and muscle sheaths. Bence-Jones' protein was constantly present in the urine over the final two years of the patient's life, but there was no rise in the blood proteins during this time. There was a moderate but progressive rise in the blood-urea, the serum calcium, and the inorganic blood phosphorus. A sternal puncture revealed numerous plasma cells.

#### *Summary*

1. Four cases of myelomatosis are described, three of the plasma cell type and one of the rare lymphocyte type (lymphocytomatosis).
2. Records of the blood proteins, serum calcium and inorganic blood phosphorus have been made in each case and the differences between the hypercalcaemia of myelomatosis and that of generalized osteitis fibrosa (von Recklinghausen) are emphasized.
3. The break-down of nucleo-proteins derived from the tumour cells is suggested as the cause of rise of blood uric acid which was observed in these cases and in several found in the literature.
4. Hyperproteinaemia, with a great rise in the globulin and fibrinogen was observed in one case, together with remarkable failure of clot retraction, autohaemagglutination, excessive rouleau formation and great increase in the sedimentation rate and plasma viscosity.
5. One case showed the association of myelomatosis with amyloidosis. This has lately attracted attention in view of the possibility of both the amyloid substance and the Bence-Jones' protein being produced from the break-down of myelomata of the plasma cell type.

The blood analyses and sternal punctures were done by Dr. Lucy Wills in the Pathological Laboratories of the Royal Free Hospital.

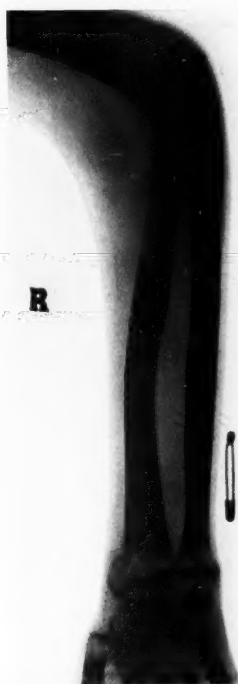
Our thanks are due to Dr. Davies, Mr. Stanford Cade, Dr. Hare, Dr. Donald Hunter, Dr. Pickard, and Professor de Wesselow for permission to publish their cases, and to Dr. Pulvertaft for the photographs and report on the amyloid nodules.

We are also indebted to Miss Vaux for the post-mortem report on Case 1, and to the Medical Unit, St. Thomas's Hospital, for the post-mortem report on Case 2. The micro-photographs were taken by Mr. Bayle at the London School of Hygiene and Tropical Medicine.

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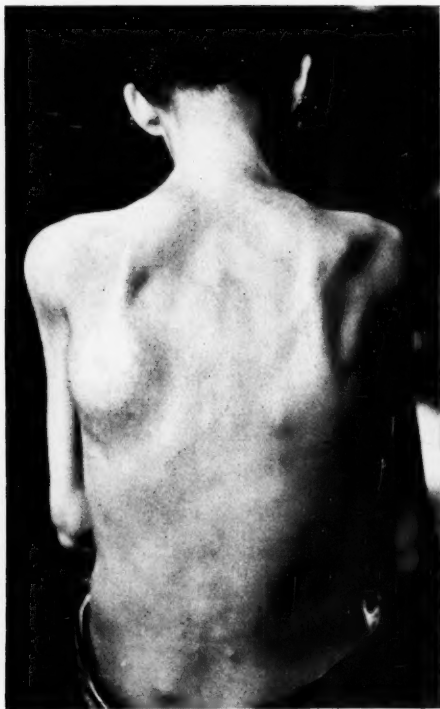
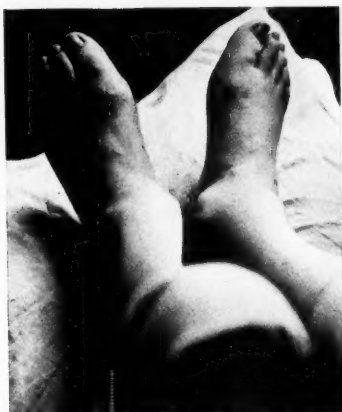




Cells from sternal puncture

Case 3. Lymphocytoma



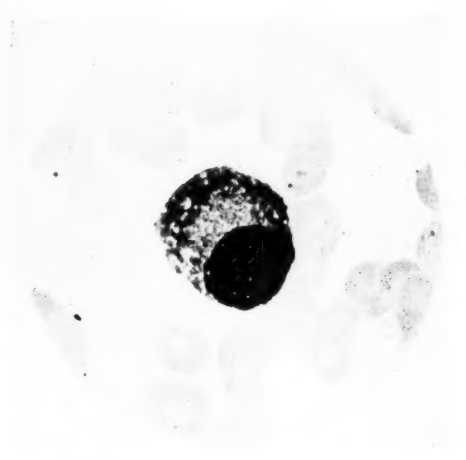


Case 4. Amyloidosis in myelomatosis

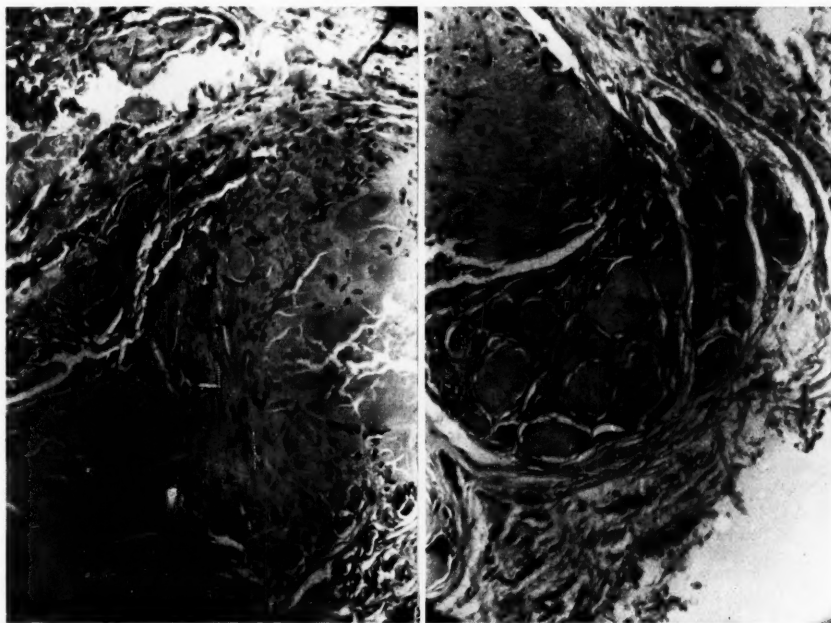




Elbow



Plasma cell from sternal puncture



Sections through amyloid nodules

Case 4



## SOME OBSERVATIONS ON THE LAEVULOSE TOLERANCE TEST<sup>1</sup>

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### *Introduction*

In 1920 Maclean and de Wesselow compared the effect of the ingestion of various sugars upon the blood-sugar level and found that in contrast to other sugars (for example, glucose) laevulose produced little, if any, increase in the total blood-sugar. Spence and Brett (1921) found that marked hyperglycaemia did, however, occur after the ingestion of 50 gm. of laevulose in cases of liver inefficiency of various types, and suggested a 'laevulose tolerance test' based on these findings for use in cases of suspected liver disease. Although the laevulose tolerance test has been employed in this form by a large number of workers [e.g. Covell (1923), Bodansky (1923), Tallerman (1923), Green, Snell, and Walters (1925), Green, McVicar, Rown-tree, and Walters (1925), Williams (1927), King (1927), Brown (1928), Hughes and Malik (1930), Joliffe (1931), and Kimball (1932)], the test has in general had a lukewarm reception. The reasons for this are not hard to find. In the first place doubts exist as to what should be taken as the criteria of normality and the normal standards proposed by various authors differ. As a satisfactory test would be of most value in those cases where liver damage is slight and cannot with certainty be recognized on clinical grounds, doubt as to the borderline of normality is obviously a serious disadvantage. Moreover, variations in the blood-sugar level due to emotional influence, diabetes, pancreatic dysfunction, and so on, may occur independently of the condition of the liver and may falsify the results, thus limiting the number of cases to which the test is applicable. Many of these objections could be overcome if, instead of the total sugar, the laevulose content of the blood were estimated. Analytical methods are now available for this estimation and a new form of the laevulose tolerance test employing one of these methods was described by Stewart, Scarborough, and Davidson (1937), who gave an account of the results obtained in 23 cases. The test in the new form has now been in use for over a year, and it is possible to give a more detailed account using the data from 130 cases.

*Theoretical considerations.* The laevulose tolerance test is based on the assumption that the liver is the main site of laevulose metabolism. In cases of liver insufficiency of any kind, therefore, it might be expected that laevulose

<sup>1</sup> Received October 8, 1937.

would be less readily dealt with by the body than it is normally. That this assumption is well justified has been shown in several ways. Various observers following Ishmori (1913) have shown that laevulose is converted into glycogen in the liver, and Cori (1925) has shown that the rate of increase of liver glycogen is greater after laevulose than after glucose administration. From the experiments of Mann and Magath (1922), who showed that the intravenous injection of laevulose was unable to prevent hypoglycaemic convulsions in moribund hepatectomized dogs, whereas glucose could do so, it can be concluded that the liver is an important site for the conversion of laevulose into glycogen. This view has received abundant support from the work of Isaac (1920), Kimball (1932), and others who have demonstrated the prolonged hyperglycaemia following laevulose ingestion in cases of hepatic disease. Bodansky (1923) produced liver damage artificially in dogs by means of chloroform, phosphorus, and hydrazine, and demonstrated a diminished laevulose tolerance in the affected animals. Although it is, therefore, apparent that laevulose metabolism takes place to a very large extent in the liver, it is also possible that laevulose may, to an important extent, be utilized directly by the tissues. Cori and Cori (1928), studying the mode of the disposal of various sugars in rats, concluded that of the total quantity of laevulose absorbed from the alimentary tract in four hours, 36 per cent. was oxidized directly, 38 per cent. converted into liver glycogen, and 12 per cent. into tissue glycogen. Steinberg (1927), from studies of carbohydrate utilization in isolated surviving tissues, demonstrated that skeletal muscle was able to utilize laevulose directly as efficiently as it could utilize glucose. This result supports McGuigan (1908) and is confirmed by Griesbach (1929) and by Bornstan and Volker (1929), who found that the isolated mammalian limb could utilize laevulose as well as, or even slightly more readily than, glucose. Griffith and Waters (1936) further suggested that laevulose must be utilized as such by the muscles and brain since it prolongs the life of eviscerated animals, although Bollmann and Mann (1931) found that animals from which the stomach, liver, and intestines had been removed succumbed rapidly to hypoglycaemia in spite of laevulose administration. On the other hand, Maclean and Smedley (1912) and Stewart and Gaddie (1934) were unable to demonstrate any utilization of laevulose by the heart-muscle of the dog, rabbit, or frog, while a similar negative result was obtained by Ashford (1933) for brain tissue. The balance of evidence suggests that laevulose may be utilized by skeletal muscle, though not to any great extent by heart muscle or brain tissue. Even if we admit the 'can', a further question of 'does' may still arise. A reaction which a tissue, especially when isolated, is capable of bringing about, is by no means necessarily one which it actually does bring about under normal conditions. The evidence of Cori that less than half as much muscle glycogen is formed from laevulose as from glucose, affords quantitative support for the view that the liver is of prime importance in the metabolism of laevulose. A complicating factor

in regard to the fate of ingested laevulose is provided by the suggestion that a small part of it may be converted to glucose before it reaches the liver. Thus Verzár and McDougall (1936) have put forward evidence to show that the conversion of laevulose to glucose may occur in the intestinal mucosa, a view supported by the work of Laszt (1933), but controverted by that of Burget, Moore, and Lloyd (1932), and Oppel (1929). Bollmann and Mann (1931) concluded from experiments on eviscerated animals that conversion of laevulose to glucose could occur in the liver although not to any marked extent in other tissues, and was independent of the pancreas. Glucose formation from laevulose by the liver has recently been demonstrated directly by Cori and Shine (1936) using liver slices in the presence of oxygen. Partial conversion of laevulose to glucose in the intestinal mucosa, in no way interferes with the laevulose tolerance test, since it merely reduces to a slight extent the amount of laevulose which is absorbed as such into the blood-stream. In this brief survey of the evidence concerning the role of the liver in laevulose metabolism, we have refrained from stressing that supplied by the laevulose tolerance test itself. Actually, the fact that the increase in total blood-sugar after laevulose ingestion is much less than that following ingestion of a similar amount of glucose, is not adequately explained by the slower absorption of laevulose. Even when the concurrent fall in the blood-glucose is taken into account (Davidson, Kermack, Mowat, and Stewart, 1936; Stewart and Gaddie, 1934), the relatively small amounts of laevulose found in the blood strongly suggest that laevulose is removed from the blood more rapidly than is glucose. When, also, it is found that this removal of circulating glucose is notably inefficient in liver disease, but not in other conditions which are expected to influence adversely the disposal of carbohydrate, the conclusion seems inevitable that the liver is of paramount importance in laevulose metabolism.

The objection has been brought against the test that variations in the total blood-sugar may occur independently of the liver and may produce fallacious results, for example, in diabetes mellitus. Indeed, the test in its old form has always necessitated exclusion of diabetes in all cases where a 'positive' result was found. By estimating blood-laevulose, however, we believe that this objection can be overcome, since there is ample evidence to show that the first stage of laevulose metabolism is not under insulin control. There are several possible ways in which the metabolism of laevulose might be accomplished. In the first place, laevulose might be utilized, as such, directly by the tissues, and there is some evidence that this does occur, although probably not to any great extent in the intact animal. Secondly, laevulose might be converted to glycogen in the liver under the influence of insulin, i.e. it would be dealt with much in the same way as ingested glucose. A third possibility is that laevulose is first converted in the liver independently of insulin into glucose, or some carbohydrate which is subsequently dealt with in the usual manner. Davidson, Kermack, Mowat, and Stewart (1936), as the result of experiments in rabbits,

hold that the metabolism takes place in two stages, firstly, a conversion of laevulose to glucose or some similar substance, *independently of insulin*, with, secondly, the disposal of this substance under the influence of insulin. This view is supported by the work of Corley (1929), Wierzechowski (1926), and Davidson, Kermack, Mowat, and Stewart (1936) who found that insulin had no effect on the rate of removal of laevulose from the blood. It has been shown repeatedly that the intravenous injection of laevulose can both relieve hypoglycaemia in animals, although taking longer to do so than glucose, and also protect animals from the effects of excessive insulin dosage. Moreover, Bollman and Mann (1931) noted the conversion of injected laevulose into glucose after extirpation of the pancreas. Furthermore, it is supported by our own results in cases of uncomplicated diabetes, where the laevulose curves are quite normal although the total sugar curves are markedly abnormal (rendering the test quite useless by the old method). The rise in the blood-sugar curve appears to be due to a rise in the blood-glucose. Such cases, therefore, provide strong evidence that the first stage of laevulose metabolism is its conversion, independently of insulin, to glucose, or some very closely allied substance. Since insulin plays no part in regulating the removal of laevulose from the blood-stream, the laevulose tolerance test in its new form is capable of giving reliable information even in cases of pancreatic dysfunction and disordered glucose metabolism from any cause.

*Technique.* Fifty gm. of laevulose were administered in each case. The sugar was dissolved in 100–200 c.c. of boiling water, the juice of half a lemon was added, and the solution was placed in a refrigerator until cold. By these methods, and by the use of pure laevulose (Griffin and Tatlock, B.P.), the drink was rendered more palatable and the nausea and alimentary disturbances noted by Folin and Berglund (1922) and by Hansen (1923) (which we had ourselves observed in early experiments) were eliminated. The taking of this solution was followed preferably by the drinking of 200 c.c. of cold water. All subjects had fasted for at least twelve hours prior to the test. A specimen of blood (4 c.c.) was taken in the fasting state, the laevulose at once administered and 4 c.c. specimens of blood were withdrawn at half-hourly intervals after ingestion for a period of two hours. The one-and-a-half hour specimen was omitted in many cases without detracting from the value of the test. The minimum of oxalate was used as anti-coagulant, and in each blood-sample total sugar was determined by the method of Hagedorn and Jensen, and laevulose by a modification of the diphenylamine method of Patterson (1935) which we have previously employed (Stewart, Scarborough and Davidson (1937). Two c.c. of blood were pipetted into a boiling tube containing 14 c.c. of water. Two c.c. of a 10 per cent. zinc sulphate solution and 2 c.c. of normal sodium hydroxide were added. After thorough mixing of the contents, the tube was heated in a water-bath at 80° for five minutes. After cooling, the mixture was filtered through a 9 cm. paper. Ten c.c. of the filtrate were acidified with two drops of 1 per cent. acetic acid, and were evaporated, by free boiling, in a test-tube graduated at 4 c.c., to just under the mark. The residual solution was then made up exactly to 4 c.c. Four c.c. of 6 normal HCl and 0.1 c.c. of 20 per cent., alcoholic diphenylamine were then added, and the tube, after shaking, was

placed in a briskly boiling water-bath for fifteen minutes. After cooling, 10 c.c. of butyl alcohol and 2 gm. of solid ammonium sulphate were added. The tube was stoppered and briskly shaken. The upper alcoholic layer was pipetted off into a centrifuge tube, about 20 mg. of anhydrous sodium sulphate were added, and, after shaking, the liquid was centrifuged for five minutes. The drying with sodium sulphate and the centrifuging made the comparison of unknown and standard in the colorimeter very much easier; when using the photometer it was essential, since the turbidity due to varying amounts of moisture in different analyses then made it impossible to measure accurately the absorption due to the colour. For colorimetry a standard was prepared by carrying out the described procedure on a fasting blood filtrate to which a suitable amount (e.g. 0.2 mg. laevulose) had been added. This, of course, necessitated a fasting blood sample of at least 4 c.c. For photometry, our usual method, a standard curve was constructed by adding known amounts of laevulose to filtrates from normal fasting blood. The best results were obtained with a filter S.53 and a stratum thickness of 20 mm. (19-98). It has been found possible now to use this method with micro-cups so that the sample of blood required for both estimations may be obtained from a finger prick. Glucose was determined by difference.

### *Results*

1. *Normal subjects.* Following Folin and Berglund (1922), most observers agree that the rise in the total blood-sugar after the administration of laevulose is considerably less than that caused by an equal amount of glucose. This difference was ascribed by Folin and Berglund to the more rapid uptake of laevulose by the tissues, a conclusion which modern methods of analysis have made untenable. Reinhold and Karr (1927) considered that laevulose was more rapidly converted into glycogen by the liver than was glucose, and also that the rate of oxidization in the tissues was possibly greater. Cori (1925) held that the difference was due to the slower absorption rate of laevulose, while Joliffe (1931) drew attention to the fact that the more rapidly a sugar is absorbed, the more strain is thrown upon the glycogenesis mechanisms, and postulated that the higher blood-sugar after glucose or galactose is due to the fact that absorption has overrun glycogenesis, whereas with a more slowly absorbed sugar such as laevulose, glycogenesis is able to proceed almost as rapidly as absorption. Davidson, Kermack, Mowat and Stewart (1936), however, in experiments on rabbits, observing the level of blood-laevulose, total sugar, and (by difference) glucose, found that the small rise in total sugar after laevulose administration could be accounted for, in part at least, by a slight fall in glucose. They suggested that although the conversion of laevulose to glucose is independent of insulin, laevulose nevertheless stimulates the pancreas to secrete insulin, and that it is this insulin which is responsible for the fall in glucose. A similar fall in glucose is shown in the tables given by Corley (1929) and also (though not explicitly stated) in the results of Scott (1935). On the other hand, van Creveld and Ladenius (1928), and Harding, Nicholson and Armstrong (1933) found that the rise in total reducing sugar after laevulose ingestion could not be accounted for wholly by the laevulose

present in the blood. Dealing with total sugar curves only, Spence and Brett (1921) regarded an increase of more than 10 mg. per 100 c.c. in the total sugar an hour after laevulose ingestion, with failure to return to normal within two hours, as indicative of liver damage (five cases), while Tallerman suggested increases up to 30 mg. per 100 c.c., or a maximum of 135 mg. sugar

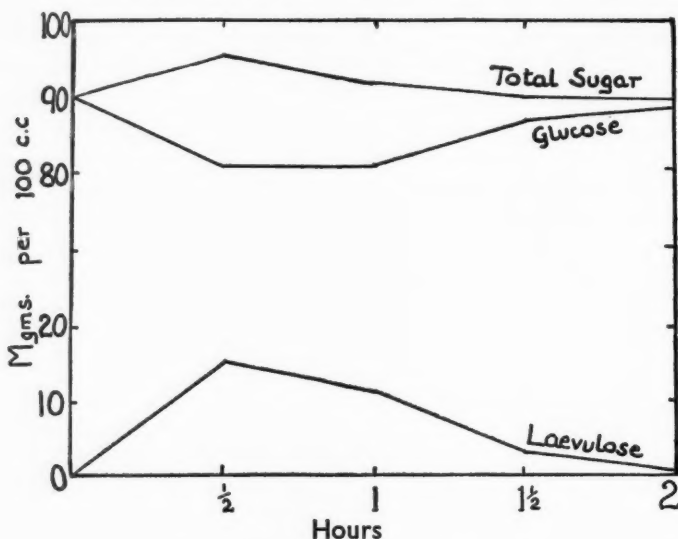


FIG. 1. Case 40. Normal subject.

per 100 c.c. as within the limits of normal (15 cases). Joliffe regarded a total blood-sugar of over 125 mg. per 100 c.c. at the end of an hour as indicative of abnormality, whatever the fasting level (81 cases). Kimball (1932) concluded that elevations of 30 mg. per 100 c.c. above the fasting level in the first specimen half an hour after laevulose ingestion, or of over 15 mg. per 100 c.c. in the second, one hour after laevulose ingestion, indicated definite hepatic insufficiency, although slightly smaller elevations could be regarded as suspicious.

During the past year we have carried out the test in its new form in over 130 subjects. The results obtained in 20 normal subjects, whose ages ranged from 20 to 40 years, are shown in Table I and a typical response is shown graphically in Fig. 1. The subjects concerned were all either healthy young adults or convalescent patients in whom there was no suspicion of liver disease or of disordered carbohydrate metabolism. It will be observed that all the results are similar and all have several features in common.

(a) The curves for total sugar show how slight is the hyperglycaemia following laevulose ingestion. In only three cases out of 20 does the maximum rise exceed 10 mg. per 100 c.c. This small rise in total sugar corresponds with the findings of previous observers, e.g. Spence and Brett, and Kimball, although the normal range is somewhat wider than is allowed for by Spence and Brett

and rather less than was required to cover the larger groups examined by Joliffe and by Kimball.

(b) The maximum values both for total sugar and for laevulose occur within the first hour after ingestion of laevulose. The maximum blood-laevulose value in the normal series lies between 5 and 18 mg. per 100 c.c., the mean value being 12.8 mg. per 100 c.c..

(c) At the end of the two hours the blood still contains traces of laevulose and readings of from 0 to 8 mg. per 100 c.c. are obtained. In view of what follows with regard to the readings obtained for fasting blood, these figures are difficult to interpret, but it is probable that they represent true laevulose values.

(d) In all cases the blood-glucose values decrease, the majority showing a tendency to return to normal within two hours. As has already been mentioned, this feature has been found by several previous observers and has been fully commented on by Davidson and his colleagues.

On the basis of these results the normal laevulose curve may be considered as showing a maximum value within one hour of ingestion of not more than 20 mg. of laevulose per 100 c.c. of blood. At the end of the second hour the curve should show a fall to a value below 10 mg. per 100 c.c. At the same time the glucose curve shows a fall below the fasting level and a return towards the normal figure at the end of two hours. It will be noted that the laevulose value in the fasting sample appears in the table as '0' in each case. This is an arbitrary figure, for in actual practice small values of between 0 and 5 mg. per 100 c.c. are frequently obtained, the average 'blank' being 2 to 3 mg. per 100 c.c. To what extent this blank value is due to oxalate is difficult to determine, but we have established that potassium oxalate is capable of causing the production of a blue colour with diphenylamine, although only in quantities much greater than those usually present in the blood samples. Indeed, Feigl and Frehden (1935) have used diphenylamine for the detection of oxalic acid, although under different optimal conditions. A very slight coloration is normally present in the butyl alcohol extract if oxalated blood is used (Radt, 1928), although it is absent when defibrinated blood is employed, but this is normally allowed for to a large extent, since the calibration curve for the photometer is prepared from solutions of laevulose in fasting blood filtrates. Although it is tacitly assumed by most workers that fasting blood contains no laevulose, there is some evidence which leads us to doubt this. The fasting blood of one of our patients (Case No. 99) gave a reading of over 5 mg. laevulose per 100 c.c. on several occasions. Hubbard and Russell (1937) have obtained somewhat similar results with fasting blood and, on the basis of a different method of analysis, consider that small amounts of laevulose are normally present in blood. The amounts they find are smaller than our average 'blank' reading (1 to 2 mg. per 100 c.c. of blood). Their conclusion is strengthened by their finding greater amounts (about 5 mg. per 100 c.c.) in normal cerebrospinal fluid. The evidence, however, is not conclusive, and the subject requires further investigation by other methods. For the purposes of

this paper we have assumed, in the absence of more definite evidence, that fasting blood contains no amount of laevulose sufficient to interfere seriously with the test, although traces may actually be present. The invariable fall in the blood-glucose is exactly similar to that found in rabbits by Davidson, Kermack, Mowat and Stewart (1936). It strongly suggests a stimulation of insulin secretion by the circulating sugar, and although, in the human subject, this effect might conceivably be ascribed to the glucose formed, according to Verzář, during laevulose absorption, that hypothesis seems unlikely, and is negatived by the fact that, in the animal experiments, laevulose was administered intravenously. An alternative view might be that glycogenesis, having once been started, proceeds indiscriminately at the expense of any monosaccharide which happens to be available; this too, though not impossible, seems unlikely in view of the very slight rise in the total sugar, with, therefore, (if other factors favouring glycogenesis be excluded) but slight stimulus to the formation of glycogen. The subjects in Table I were all within the age period 20 to 40 years. In Table II are given the results obtained from ten normal subjects, all of whom were over 50 years of age. It will be observed that, with the exception of Case 61, the total sugar curves and the laevulose curves resemble closely those obtained from younger persons.

The total sugar curves rise to a maximum, within an hour, of less than 30 mg. per 100 c.c. above the fasting level. The laevulose curves reach a maximum of about 10 mg. per 100 c.c. within an hour, but the figures at the end of two hours are rather higher than is the case with younger subjects. The glucose curve, however, rises above the fasting level in each case and then gradually returns towards it. (See Fig. 2.) Why the glucose curve should rise in elderly subjects and fall in younger ones is difficult to explain. Tables I and II agree in showing that, so far as the laevulose is concerned, whether the subject is old or young, the criterion of normality is the same—the laevulose curve reaches a maximum value of less than 20 mg. per 100 c.c. within the first hour and then gradually falls. Where old age is complicated by marked arterial disease, another state of affairs obtains, as will be seen later. According to Tallerman's standard of normality, a rise of 30 mg. per 100 c.c. in the total blood-sugar was considered to be the highest value allowable for a normal tolerance. That mistakes could easily be made in both directions if this criterion alone is applied, is evident from a consideration of Cases No. 9 (Table III) and No. 72 (Table XII). Table III shows the result of the test in three cases of anxiety neurosis. Case No. 9, a male of 24, gave results which, if interpreted by the total sugar curve alone, would indicate some disturbance of liver function. Estimation of the blood-laevulose, however, reveals a normal laevulose curve, and shows that the increase in total blood-sugar is entirely due to an abnormal rise in blood-glucose. In Case No. 72 there was definite evidence of liver damage, but the total sugar curve comes just within Tallerman's standard of normality. The laevulose curve, however, reveals disturbed liver function. In its new form, therefore, the test has definite advantages in that variations in the total blood-sugar, due to extraneous

causes, e.g. emotional upset, can be neglected since attention is focused on the laevulose curve which is independent of these influences. The fact that the new method detects abnormalities, which would have escaped notice by the old, is perhaps more important than the fact that it also shows normal

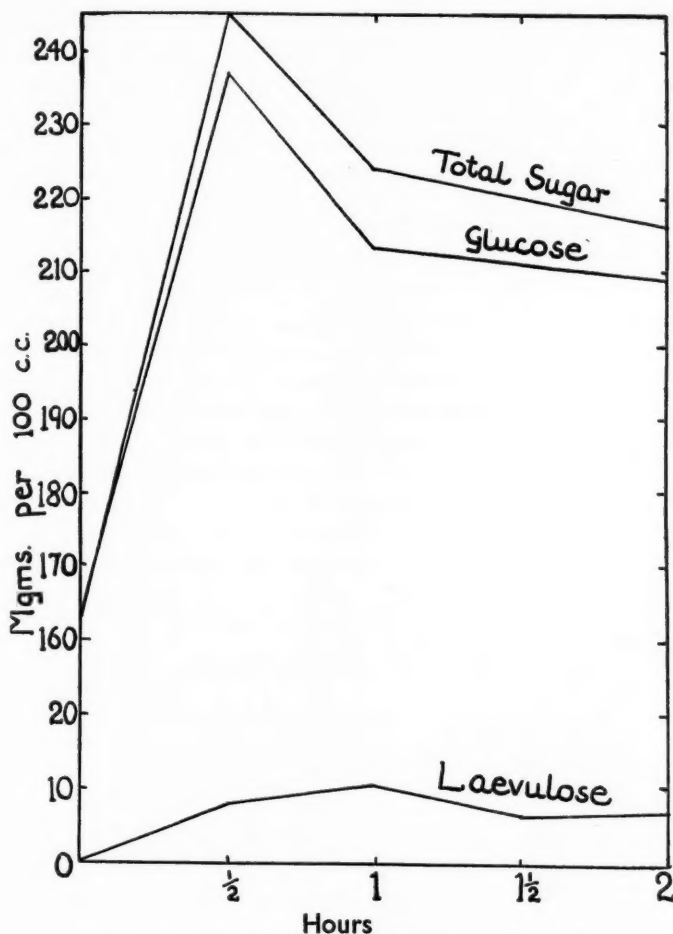


FIG. 2. Case 133. Diabetes mellitus (uncomplicated).

liver function in cases of neurasthenia, diabetes, and other endocrine disturbances which, in the old test, gave abnormal results. For in these a careful and detailed clinical examination would have disclosed the interfering condition. The exclusion of both fallacies by the new test is, however, of use, since it now becomes possible (which it was not before) to detect liver insufficiency by the aid of the laevulose tolerance test even in the presence of these other disturbances of carbohydrate metabolism.

2. *Diabetes mellitus and other glycosurias.* The results of the test in nine cases of uncomplicated diabetes are given in Table IV, and a typical curve is shown in Fig. 2. In each of them the laevulose curve shows a maximum value within normal limits, while the total sugar curves rise to high levels showing, at the maximum, an increase of well over 30 mg. per 100 c.c., and in the more severe cases showing little tendency to return to the fasting level. It is evident that the test in its old form would have been useless in such cases. The fact that the total sugar, and therefore the glucose curves, rise to abnormally high values suggests that glucose, or some very similar substance, is produced from laevulose independently of insulin and is dealt with rather inefficiently, as we should expect, by the diabetic. It is not possible to say that the reducing substance in the blood of these cases, though apparently formed from laevulose, is actually glucose itself, for the method of estimation is not specific for glucose. The rapid rise in the total sugar suggests further that this primary change in the laevulose is a fairly rapid process—as one would imagine from the low concentrations reached by the blood-laevulose itself. Since normal laevulose curves are obtained in the diabetic patient and since this fact can be explained on theoretical grounds, it is apparent that the scope of the laevulose tolerance test can be greatly extended in its new form and that one of the gravest fallacies of the test in its older form is removed. We shall show later the results of the application of the test to cases of liver insufficiency complicated by diabetes.

*Case 16.* Female. Aged 40. Diabetic for twelve months. Stable on Cals. 1956. Carbohydrate 101 gm.

*Case 18.* Male. Aged 35. Diabetic for two years. Stable on Cals. 2859. Carbohydrate 132 gm. Insulin 32–32.

*Case 24.* Male. Aged 53. Diabetic for six years. Stable on Cals. 2833. Carbohydrate 170 gm.

*Case 34.* Male. Aged 62. Diabetic symptoms for three weeks. Stable on Cals. 2100. Carbohydrate 85 gm. Insulin 15–10. Radial arteries thickened and calcified. Blood-pressure 230/115. Wassermann reaction negative. *Diagnosis:* diabetes mellitus and arteriosclerosis.

*Case 60.* Female. Aged 72. Diabetes for fifteen years. Stable on Cals. 1518. Carbohydrate 80 gm. Insulin 15–15. Dysuria for three weeks. Urea N. = 36 mg. per cent. Urea range impaired. Radial arteries not thickened. Blood-pressure 126/76. *Diagnosis:* diabetes mellitus and pyelocystitis.

*Case 132.* Female. Aged 57. Diabetic for seven years. Stable on Cals. 1871. Carbohydrate 111 gm. Insulin 8–8.

*Case 133.* Female. Aged 63. Diabetic for eight years. Stable on Cals. 1625. Carbohydrate 101 gm. No insulin.

*Case 135.* Male. Aged 57. Diabetes for one year. Stable on Cals. 2357. Carbohydrate 200 gm. No insulin.

*Case 137.* Female. Aged 35. Diabetic for twelve years. Stable on Cals. 1814. Carbohydrate 124 gm. Insulin 18–5–18.

*Case 109* is interesting. The patient, a man of 36, was found on medical examination for Life Assurance to have glycosuria. There were no other symptoms, or signs, of diabetes and a blood-sugar examination, after ad-

ministration of 50 gm. of glucose, gave on two occasions a curve which, though starting above the normal fasting level, and returning to the fasting level only in two hours after an abnormally high rise, was considered to be of the 'lag' rather than the diabetic type. The results of the laevulose tolerance test, however, revealed that the total sugar curve showed only a very slight rise and the glucose curve fell. These curves, therefore, had nothing in common with those obtained in cases of diabetes. The laevulose curve, however, rose to a maximum of 26. Using our standard of normality, this would indicate definite disturbance of liver function, and it is possible that the 'lag' type of curves obtained with the glucose tolerance test were due to diminished power of glycogenesis of a slightly damaged liver. The 'lag' curve in the glucose tolerance test is usually interpreted as indicating delayed glycogenesis and it has been suggested that this may be associated, in some cases at least, with abnormal or deficient liver function in other respects. We are at present accumulating data regarding the response to the laevulose tolerance test in patients who give definite or dubious 'lag' curves in the glucose tolerance test.

3. *Hepatic dysfunction.* As might be expected, liver insufficiency may be suspected on clinical grounds (e.g. marked enlargement), without disturbance of liver function being revealed by the laevulose tolerance test. Table V indicates the response obtained in four cases of cardiac failure, all with enlargement of the liver. In only two cases is the laevulose curve abnormal, and in these two the limit of normality is only just exceeded. All the patients showed venous congestion, but in none was there jaundice. This suggests the possibility that disturbance of the laevulose tolerance test may not occur until the excretory mechanism of the liver is impaired. The suggestion has indeed been made that the laevulose test (in its older form) shows the most marked disturbance in those patients who are jaundiced. Several of our cases reveal, however, that impairment of laevulose tolerance is not necessarily associated with jaundice, and a similar lack of correlation between the degree of impairment of laevulose tolerance and the icteric index is shown in subsequent results. For example, the laevulose curve in Case 8 (Table XV) indicates definite impairment of laevulose tolerance, although jaundice was absent, while in Case 42 (Table VIII), where the icteric index was 115, the laevulose curve is normal.

*Case 14.* Male. Aged 66. Severe exertion dyspnoea for eighteen months. Cough, flatulent dyspepsia, orthopnoea, cyanosis, considerable oedema, and bilateral hydrothorax. No ascites or jaundice. Liver enlarged two inches below costal margin, regular, firm, and tender. Blood-pressure 164/90. Radial arteries markedly thickened. *Diagnosis:* arteriosclerosis; hypertensive cardiac failure.

*Case 15.* Male. Aged 56. Exertion dyspnoea and oedema for eighteen months. Orthopnoea, cyanosis, and marked oedema. Pulse regular. Apex beat in anterior axillary line. Tic-tac rhythm. Liver enlarged 2½ inches below costal margin, tender, smooth, and regular. Ascites, but no jaundice. Wassermann reaction positive. Argyll-Robertson pupils.

Radial arteries not thickened. Blood-pressure 130/74. *Diagnosis*: syphilitic myocarditis.

*Case 19.* Aged 16. Dyspnoea on exertion with cyanosis and oedema for one year. No ascites or jaundice. Radial arteries not thickened. Blood-pressure 126/80. Liver four inches enlarged, smooth, regular, and slightly tender. *Diagnosis*: mitral stenosis and incompetence; congestive cardiac failure.

*Case 20.* Female. Aged 41. Exertion dyspnoea for six months. Patient very cyanosed, severely orthopnoeic, and very drowsy. Moderate oedema and slight ascites. No jaundice. Liver five inches enlarged, smooth, regular, and tender. *Diagnosis*: mitral stenosis and incompetence; congestive cardiac failure.

4. *Toxic jaundice.* The results of the test in four cases of toxic jaundice are shown in Table VI. In three out of the four cases the laevulose curve indicates definite abnormality of liver function. Case 5 is of interest in that it demonstrates the greater delicacy afforded by direct laevulose estimation in attempting to assess liver damage. The patient, a man aged 42, developed jaundice while undergoing treatment with arsenicals for syphilis. The liver was enlarged and tender and was palpable  $1\frac{1}{2}$  inches below the costal margin. The van den Bergh reaction gave a positive biphasic result and the icteric index was 70. The laevulose tolerance test at this time (curve *a*) gave a border-line result on the total sugar curve, but the laevulose curve was definitely abnormal. A month later the icteric index had fallen to 24 and the liver was no longer enlarged or tender. Both sets of figures (curve *b*) now fall well within normal limits. The results in this case of metallic poisoning are similar to those obtained experimentally by Bodansky (1923). He found a diminished laevulose tolerance in dogs with liver insufficiency, experimentally produced by chloroform, phosphorus, and hydrazine, and a return to normal tolerance on recovery. Case 95 illustrates the development of impaired laevulose tolerance with the onset of jaundice. The patient was a man, aged 71, with emphysema and pyonephrosis, who gave perfectly normal laevulose and total sugar curves (curve *a*). The glucose curve rises, but this is usual in elderly patients. Septicaemia and toxic jaundice, however, developed and curve *b* was then obtained indicating severe impairment of laevulose tolerance (Fig. 3).

*Case 28.* Male. Aged 41. Arsenical jaundice during antisyphilitic treatment. Liver  $\frac{1}{2}$  inch below costal margin.

*Case 123.* Male. Aged 37. Arsenical jaundice during antisyphilitic treatment. Liver  $1\frac{1}{2}$  inches below costal margin, and tender. Icteric index 38.

5. *Catarrhal jaundice.* In cases of acute hepatitis one might expect a marked disturbance of liver function. Table VII shows the results obtained in eight cases. It will be observed that only four cases, Nos. 17, 78, 103, and

110 are abnormal, while one, No. 79, is a border-line case. In only one, Case 78, is the disturbance of the laevulose curve marked and there is no relationship between the maximum rise in blood laevulose and the degree of jaundice.

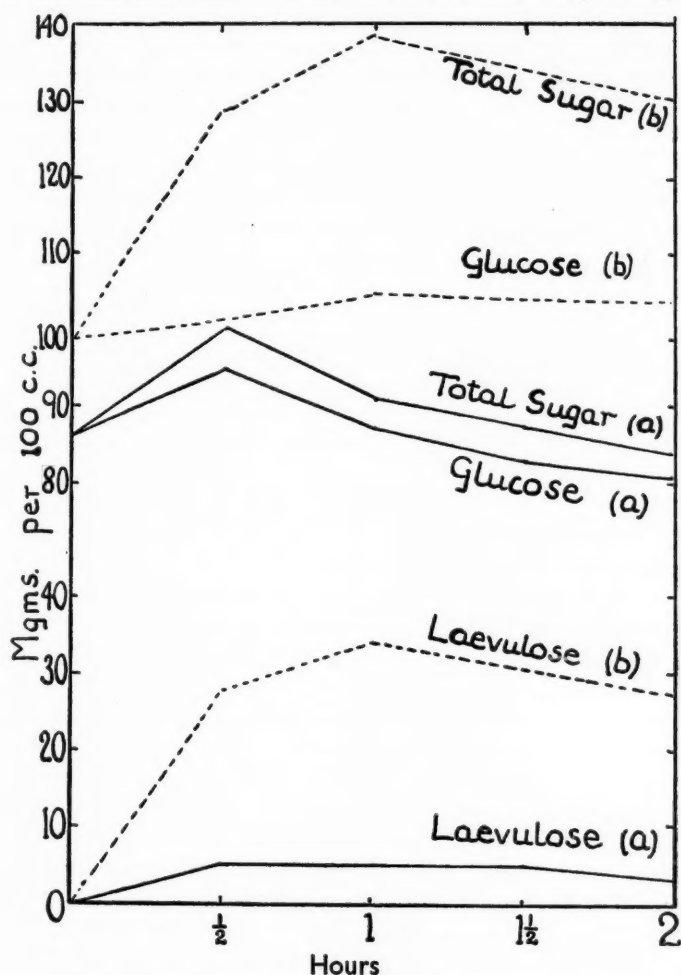


FIG. 3. Case 95. (a) before, and (b) during toxic jaundice.

Indeed, Case 33, with the highest icteric index (164), gave normal curves for both laevulose and total sugar. It is not altogether unexpected that apparently normal curves are obtained in some cases where clinical signs suggest liver dysfunction. At present we are unable to estimate the amount of liver damage which must be present before diminished laevulose tolerance is manifested, nor are we able to distinguish between generalized and localized liver damage. It is certain that the liver has considerable reserve powers. Indeed, Mann (1925 *a, b, c*) found that removal of four-fifths of

the liver affected dogs but little, but Kimball has pointed out the difference between one-fifth of a healthy liver, and an entire liver all of which is even mildly diseased. Rosenthal (1922), using the phenoltetrachlorophthalein test, has been able to detect the removal of 12 per cent. of the liver in rabbits, and from our experience we have no reason to believe that this test is superior to the laevulose tolerance test. It is important to remember, however, in dealing with an organ such as the liver, which possesses a large number of unrelated functions, that a disturbance of one function, even though it be marked, does not necessarily mean a disturbance of all. That this is true is indicated by the lack of correlation between our results with the laevulose tolerance test and the depth of jaundice present at the time.

*Case 17.* Male. Aged 60. Headache, pains in the back, jaundice for five weeks, liver just palpable and tender. Icteric index under 30. Van den Bergh test: biphasic reaction. Wassermann: negative.

*Case 33.* Male. Aged 31. Anaemia and flatulence for three weeks. Jaundice for fourteen days. Liver  $2\frac{1}{2}$  inches below costal margin, firm, regular, and not tender. Icteric index 164. Van den Bergh test: biphasic reaction. Wassermann: negative.

*Case 52.* Male. Aged 69. Abdominal pain for three months. Severe epigastric pain, vomiting, and jaundice for seven days. Liver enlarged one inch, firm, and very tender. Icteric index 24. Van den Bergh test: biphasic reaction. Wassermann: negative.

*Case 75.* Female. Aged 16. Pain in right side of abdomen and sickness for three weeks; jaundice for eighteen days. Liver not enlarged, but tender on deep palpation. Icteric index 31. Van den Bergh test: biphasic reaction. Wassermann: negative.

*Case 78.* Female. Aged 30. Jaundice and lack of energy for one week. Liver  $\frac{1}{2}$  inch enlarged and tender. Icteric index 36. Van den Bergh test: biphasic reaction. Wassermann: negative.

*Case 103.* Male. Aged 31. Jaundice for five weeks. Epigastric fullness, nausea, and anaemia. Febrile. Icteric index 57. Van den Bergh test: biphasic reaction. Liver not palpable. Tenderness in right hypochondrium on deep palpation.

*Case 110.* Male. Aged 23. Jaundice for six weeks. Pain between shoulders. Anaemia, nausea, and vomiting. Attack of severe abdominal pain simulating biliary colic. Liver not palpable. Tenderness and slight rigidity in right hypochondrium. No evidence of gall-stones. Wassermann: negative.

6. *Obstructive jaundice.* Obstructive jaundice might be expected to be associated with varied degrees of inefficiency on the part of the liver cells to deal with laevulose. The results given in Table VIII indicate that various degrees of disturbance of the laevulose curve have been found ranging from the normal curve of Case 86 to the grossly abnormal one of Case 104. This series of cases further confirms the view that there is no relationship between the disturbance of laevulose tolerance and the depth of the jaundice as

measured by the icteric index. The laevulose figures exceed the normal in all cases, except Nos. 26, 42, 43, 46 *b*, and 86, and are suspicious in Case 134. Four of these cases, however, present an interesting feature not so far noted, that, although the laevulose figures may be considered normal, the total sugar curve rises to values in excess of normal, indicating a probable impairment in glycogenesis on the part of the liver, or an insufficient insulin production by the pancreas. It may be noted that in Cases 34, 36, and 43 the pancreas was the seat of malignant disease, whereas in Case 42 the diagnosis was carcinoma of the common bile-duct. Case 46 also reveals an improvement in hepatic function after laparotomy, associated with a slight decrease in the depth of the jaundice, whereas the pancreatic insufficiency remains. Without more evidence than is at our disposal it is not possible to decide between these hypotheses. It does not seem probable that gross impairment of the glycogen-forming power of the liver would exist without disturbance of other functions related to carbohydrate metabolism, and in these cases laevulose did not accumulate as such in the blood. Hence its conversion to glucose (or similar substance) was proceeding normally, and we have advanced evidence suggesting that this change occurs largely in the liver. On the other hand, carcinoma involving the pancreas may well interfere with insulin supply, and it is known that carcinoma of the common bile-duct is frequently associated with some sclerosis of the head of the pancreas. Hence we incline to the view that the raised glucose in these cases is probably to be ascribed to interference with the supply of insulin. The increase in glucose was not confined to those cases showing normal laevulose curves, but actually appeared in 14 of the 16 cases in this group. It is, in fact, of fairly common occurrence whenever the laevulose curve is abnormally raised (it occurs in 42 out of 62 non-diabetic cases), and may then be interpreted as showing a general disturbance of the liver carbohydrate metabolism. In a few of these cases, too, it is possible that abnormalities of the insulin supply may be concerned, since some of them were due to carcinoma involving the pancreas or the common bile-duct. There does not, however, seem to be any correlation between the degree of abnormality of the laevulose curve and the increase in glucose. This in itself suggests that more than one factor is concerned in the glucose metabolism following laevulose ingestion, so that the interpretation of these curves must depend on different factors in different groups of cases.

*Case 26.* Male. Aged 50. Jaundice for two days, due to gall-stones which were ultimately passed. Bile in urine. Wassermann: negative. Blood-pressure 125/80. Arteries not palpable. *Diagnosis:* obstructive jaundice due to gall-stones (radiological).

*Case 42.* Male. Aged 62. Increasing jaundice and loss of weight for two months. Liver thought to be enlarged, tumour in right hypochondrium projecting far below costal margin. Icteric index 113. Van den Bergh test: immediate direct. Wassermann: negative. Blood-pressure 98/64.

*Diagnosis*: primary carcinoma of common bile-duct with obstructive jaundice (operation).

*Case 43.* Female. Aged 73. Weakness and loss of weight for one month. Flatulent dyspepsia, thirst, polyuria and glycosuria. Diet: Cals. 1518, carbohydrate 78 gm. Insulin 10-10-10. Patient had been jaundiced for five weeks. Icteric index 150. Van den Bergh: immediate direct reaction. Vague mass in epigastrium with tenderness on deep palpation. No enlargement of spleen. Radial arteries not thickened. Blood-pressure 120/68. Wassermann: negative. *Diagnosis*: Carcinoma of pancreas; diabetes mellitus; obstructive jaundice (clinical).

*Case 46.* Female. Aged 51. Jaundice, indigestion, and loss of weight for five weeks. Liver not enlarged, but tender on deep pressure. No palpable mass associated with it. Icteric index 162. Van den Bergh test: biphasic reaction. Wassermann: negative. Curve (a) was obtained. A laparotomy was then performed and twelve days later the second curve (b) was obtained. Icteric index 149. *Diagnosis*: adeno-carcinoma of pancreas; obstructive jaundice (operation).

*Case 52.* Female. Aged 61. Constipation, flatulent dyspepsia, and jaundice for two months. Liver enlarged and tender. Icteric index 28. Van den Bergh test: delayed direct. Wassermann: negative. *Diagnosis*: stone in common bile-duct; obstructive jaundice (clinical).

*Case 69.* Male. Aged 55. Attacks of upper abdominal pain for many years. Liver one inch enlarged. Icteric index 120. Van den Bergh test: biphasic. Wassermann: negative. Radial arteries not thickened. Blood-pressure 130/90. *Diagnosis*: cholecystitis and cholangitis; gall-stones; obstructive jaundice (operation).

*Case 74.* Male. Aged 38. Pain in abdomen, diarrhoea, loss of weight, and jaundice for five weeks. Liver enlarged two inches. Icteric index 138. Van den Bergh test: immediate direct. *Diagnosis*: carcinoma of hepatic duct, obstructive jaundice (operation).

*Case 81.* Male. Aged 79. Constipation with attacks of diarrhoea, loss of weight, and vomiting for six weeks. Jaundice for three weeks. Liver one inch enlarged. Icteric index 110. Van den Bergh test: biphasic. *Diagnosis*: carcinoma of biliary passages; obstructive jaundice (clinical).

*Case 85.* Female. Aged 61. Diabetic symptoms for three years. Jaundice, pain in right hypochondrium, and vomiting for nine days. Liver two inches enlarged. Gall-bladder palpable. Palpable mass in epigastrium. Icteric index 57. Wassermann: negative. Radial arteries thickened. Blood-pressure 124/68. *Diagnosis*: cholecystitis and gall-stones; diabetes mellitus; obstructive jaundice; ?carcinoma of pancreas (clinical, radiological).

*Case 86.* Female. Aged 57. History of jaundice at each confinement. Pain in upper abdomen in right side for ten days. Liver two-and-a-half inches below costal margin. Very tender. At operation: stone in common bile-duct; liver apparently normal. *Diagnosis*: cholecystitis and gall-stones; obstructive jaundice.

*Case 87.* Male. Aged 80. Jaundice, flatulent dyspepsia, loss of weight for fourteen days. Liver not palpable. Icteric index 134. Van den Bergh test: biphasic. Wassermann: negative. Radial arteries thickened. Blood-pressure 130/75. *Diagnosis*: carcinoma of head of pancreas with obstructive jaundice (clinical).

*Case 104.* Male. Aged 48. Intermittent attacks of pain in right hypochondrium for twenty years. Biliary colic followed by jaundice for fourteen

days. Icteric index 125. Van den Bergh test: biphasic. Liver and gall-bladder not palpable. Tenderness over gall-bladder. *Diagnosis*: gall-stones; obstructive jaundice (clinical).

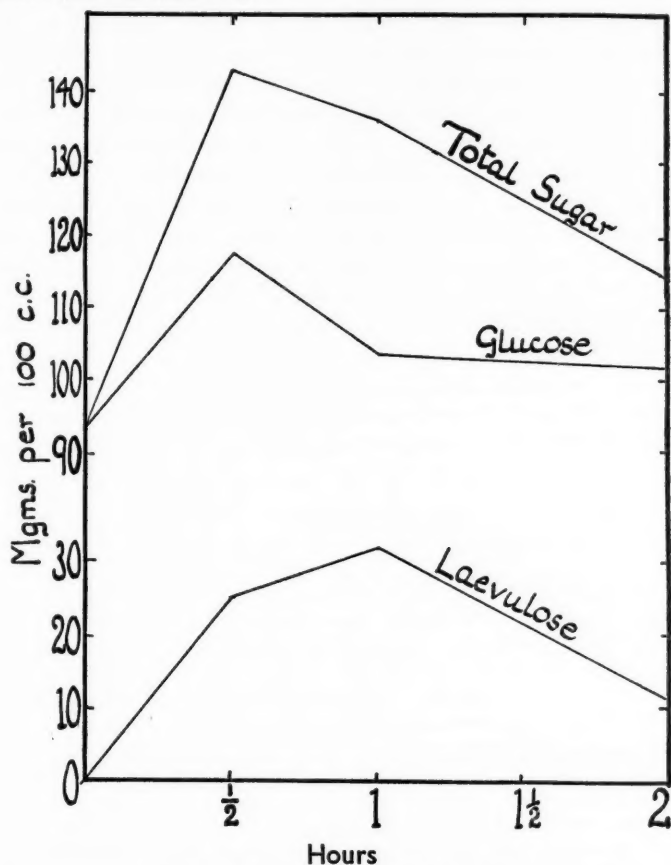


FIG. 4. Case 70 b. Alcoholic cirrhosis.

7. *Cirrhosis of the liver.* The results obtained in 16 cases of cirrhosis of the liver are given in Table IX and a typical curve (Case 70 b) is shown in Fig. 4. In all but five (Nos. 48, 56, 58, 65, and 66) the laevulose curve is abnormal. In Cases 21 and 45 there was no history of alcoholism, but both were diagnosed clinically as cirrhosis, the diagnosis in Case 21 being confirmed at autopsy; both subjects were jaundiced, and show an abnormal response. Cases 65 and 66 both gave a history of prolonged and excessive consumption of alcohol, both had haematemesis on admission to hospital, and at the time of the laevulose tolerance test were regarded as possible early cases of cirrhosis. Neither case was jaundiced, nor was the liver enlarged. The laevulose curve is normal in both, but again we found an excessive rise in the total blood-sugar values due to the fact that the blood

glucose was abnormally increased. The lack of clinical evidence of cirrhosis in these cases and the normal laevulose response weigh heavily against a diagnosis of cirrhosis, and indeed the final diagnosis in Case 65 was confirmed as peptic ulcer. Cases 48 and 56, diagnosed clinically as alcoholic cirrhosis, gave normal responses, although the total sugar values of Case 56 attain a suspiciously high maximum. Case 56 is another example of a patient with a history of dyspepsia and haematemesis on admission, in whose case the laevulose tolerance test gives evidence against a diagnosis of cirrhosis.

The test was performed on two occasions on Case 70, at an interval of one month. The higher figures in the second test coincide with deterioration in the clinical condition. Case 90 gave no alcoholic history and there was little clinical evidence to suggest cirrhosis. The laevulose curve, however, was abnormal, and a diagnosis of cirrhosis was subsequently made at operation. The value of the test in such a case is obvious. In Cases 112 and 113 there was no alcoholic history and the diagnosis of cirrhosis is based on rather flimsy clinical evidence. In Case 112 the laevulose curve just reaches the limit of normality and gives no strong support for a diagnosis of cirrhosis. In Case 113 the laevulose curve is decidedly abnormal, but the patient also suffered from arteriosclerosis. As will be seen later, such cases very often show an abnormal laevulose tolerance, and a diagnosis of liver dysfunction must be made with caution.

*Case 21.* Male. Aged 34. Seven attacks of haematemesis during the last four years. Nausea and vomiting and pain in right hypochondrium with jaundice for fourteen days. No alcoholic history. Icteric index 108. Van den Bergh test biphasic. Liver two inches enlarged. Very tender and irregular. Ascites. *Diagnosis:* cirrhosis of liver (confirmed at autopsy).

*Case 37.* Male. Aged 49. Alcoholic history. Pain in upper abdomen, loss of appetite, attacks of nausea, and vomiting for four months. Liver seven inches below costal margin, smooth, firm, and tender. Ascites. Radial arteries not thickened. Blood-pressure 136/80. Icteric index 11. Wassermann: negative. *Diagnosis:* alcoholic cirrhosis; incipient delirium tremens.

*Case 45.* Female. Aged 31. Admitted suffering from acute lobar pneumonia. Had been slightly yellow since birth of child five years ago. Jaundice more intense with pneumonia, and persisted till discharge. No alcoholic history. Liver reduced in size. Ascites. Icteric index 20 (had been 44 one month previously). Van den Bergh test: biphasic. Blood-pressure 98/60. No evidence of renal disease. *Diagnosis:* cirrhosis of liver.

*Case 48.* Male. Aged 53. Alcoholic history. Dyspnoea on exertion and oedema of the feet for one month. Abdominal pain for four days. No jaundice. Liver three inches below costal margin, smooth, hard, and tender. Radial arteries not thickened. Blood-pressure 140/70. *Diagnosis:* alcoholic cirrhosis.

*Case 54.* Male. Aged 58. A heavy drinker. Dyspnoea on exertion, cough and oedema of feet for fourteen months. Jaundice for two months. Liver two inches below costal margin, tender, and regular. Moderate ascites. Mitral stenosis and incompetence. Auricular fibrillation. Radial arteries not thickened. Blood-pressure 120/80. *Diagnosis:* cardiac failure; alcoholic cirrhosis.

*Case 56.* Male. Aged 51. Alcoholic history. Pain after meals for two years. Haematemesis and melaena on admission. No jaundice. Liver not enlarged. Radial arteries not thickened. Blood-pressure 145/106. *Diagnosis:* alcoholic cirrhosis; incipient delirium tremens.

*Case 58.* Male. Aged 54. Morning sickness, flatulence and anorexia for four weeks. Swelling of abdomen and right leg for fourteen days. Loss of weight. Cyanosis. No jaundice. Liver two inches enlarged; hard and irregular. Slight ascites. Radial arteries thickened. Blood-pressure 152/88. *Diagnosis:* cirrhosis of liver.

*Case 65.* Male. Aged 37. Heavy spirit drinker for last five years. Periodic epigastric pain related to food for seven years. Haematemesis on admission. No jaundice. No enlargement of liver. No ascites. Achlorhydria. No radiological evidence of ulcer. Blood-pressure 120/50. *Diagnosis:* provisional—alcoholic cirrhosis; final—peptic ulcer.

*Case 66.* Male. Aged 37. Moderate spirit drinker. Haematemesis and melaena eleven days before test. No jaundice. No enlargement of liver. Radial arteries not thickened. Blood-pressure 116/60. *Diagnosis:* chronic alcoholism.

*Case 68.* Male. Aged 33. Excess alcohol consumption for fifteen years. Gradually increasing jaundice with remissions for two years. Loss of weight. Liver  $\frac{1}{2}$  inch below costal margin. Regular and tender. No ascites. Icteric index 100. Van den Bergh test: biphasic. Blood-pressure 128/80. *Diagnosis:* alcoholic cirrhosis.

*Case 70.* Male. Aged 60. Alcoholic history. Dyspnoea on exertion for four months. Swelling of legs and abdomen for one month. No jaundice. Liver three inches below costal margin, firm, irregular, and tender. Ascites. Radial arteries not thickened. Blood-pressure 144/90. The laevulose tolerance test was repeated (curve *b*) one month later when there was marked asthenia, loss of weight, and ascites. Jaundice. Icteric index 40. *Diagnosis:* alcoholic cirrhosis.

*Case 90.* Male. Aged 35. No alcoholic history. Swelling of stomach and dyspnoea on exertion for five years. Intermittent attacks of jaundice lasting three weeks. Patient has lived in the East and has had beri-beri, bacillary dysentery, and sand-fly fever. Laparotomy performed on account of acute abdominal pain. At operation liver was found to be 'contracted and in a state of "hob-nail" cirrhosis.' *Diagnosis:* cirrhosis of liver.

*Case 106.* Male. Aged 62. Heavy spirit drinker till five years ago. Jaundice and pain in the right side for two months. Vague epigastric pain and discomfort intermittently for four years. Liver  $1\frac{1}{2}$  inches enlarged, smooth, regular, and tender. No ascites. Icteric index 60. Van den Bergh test biphasic. Radial arteries thickened. Blood-pressure 220/120. *Diagnosis:* alcoholic cirrhosis.

*Case 112.* Male. Aged 47. No alcoholic history. No jaundice. Upper abdominal pain and vomiting, relieved by alkalis. Intermittent blood in stools. Liver just palpable below costal margin; its edge hard and regular, not tender. Radial arteries slightly thickened. Blood-pressure 150/88. *Diagnosis:* peptic ulcer; early cirrhosis of liver.

*Case 113.* Male. Aged 51. No alcoholic history. Upper abdominal pain for eighteen years, relieved by alkalis. Flatulent dyspepsia. Anorexia. Constipation. No jaundice. Haematemesis and melaena on one occasion. Liver just palpable; tender. No hyperchlorhydria; ulcer crater visible. Radial arteries thickened. Blood-pressure 208/120. *Diagnosis:* ? cirrhosis of liver; duodenal ulcer; arteriosclerosis.

*Case 130.* Male. Aged 57. Heavy spirit drinker. Epigastric pain for four months. Flatulence. Red blood passed per rectum four days before admission. No jaundice. Liver two inches below costal margin. Hard and apparently regular, not tender. No ascites. Arteries not thickened. Blood-pressure 124/80. *Diagnosis:* alcoholic cirrhosis.

8. *Syphilitic cirrhosis.* As only two cases of syphilitic cirrhosis have, so far, been examined, it is not possible to draw any definite conclusions as to the disturbance of laevulose tolerance in this condition. The results are shown in Table X. The abnormal laevulose tolerance curve in Case 38 was associated with a much less favourable clinical condition than in Case 91, where the laevulose curve is just within the limits of normality, although the total sugar curve shows a persistent rise.

*Case 38.* Considerable hepatic enlargement. Marked ascites and oedema of the legs. Secondary anaemia. Icteric index 85.

*Case 91.* Male. Aged 69. Jaundice for three weeks. Wassermann positive. No antisyphilitic treatment. Liver three inches enlarged, regular and tender. No ascites. Icteric index 30.

9. *Hepato-lienal fibrosis.* It is now generally accepted that the splenic enlargement of Banti's disease or splenic anaemia is secondary to, or at any rate accompanied by, hepatitis. McMichael (1934) has described the pathological changes which are present in the liver in a large number of cases of this condition (83 per cent. in his series). He says 'A liver which appears normal to the naked eye may yet show pronounced damage and inflammatory reaction microscopically.' McMichael found pathological evidence of hepatitis even in early cases of splenic anaemia. We have examined four such cases by the laevulose tolerance test, the results being set out in Table XI.

*Case 96.* Female. Aged 58. Intermittent attacks of diarrhoea with melaena for three years. Loss of weight. No jaundice. Liver not enlarged. Spleen reached umbilicus; firm and tender. Ascites. Superficial venous dilatation. Red blood cells 2,400,000 per c.mm., Hb. 50 per cent. Colour index 1.02. Blood-pressure 160/97. Wassermann: negative. *Diagnosis:* Banti's disease.

The figures obtained from this patient, three years after her symptoms began, are shown in Table XI. The liver was not enlarged and there was no jaundice, yet marked hepatic dysfunction is indicated by the laevulose tolerance test.

*Case 97.* Female. Aged 17. Jaundice for three months. Nausea for several weeks. Pain in upper abdomen. Remittent temperature. Spleen and liver just palpable. Icteric index 15. Blood-stained diarrhoea two weeks before test. Red blood cells 3,400,000 per c.mm., Hb. 71 per cent. A fortnight after the first laevulose tolerance test (curve *a*) the patient was discharged much improved, but the spleen now extended one inch below the left costal margin. The liver was as before. The test was repeated two weeks later (curve *b*), when liver and spleen were unchanged. *Diagnosis:* Banti's disease. See Fig. 5 for laevulose tolerance tests.

This patient's first symptom occurred only three months before the

performance of test *a*. The liver was just palpable and the patient slightly jaundiced and febrile. Again marked disturbance of hepatic function is revealed. Five weeks later, when the patient's clinical condition showed considerable improvement, curve *b* was obtained. The condition of the liver

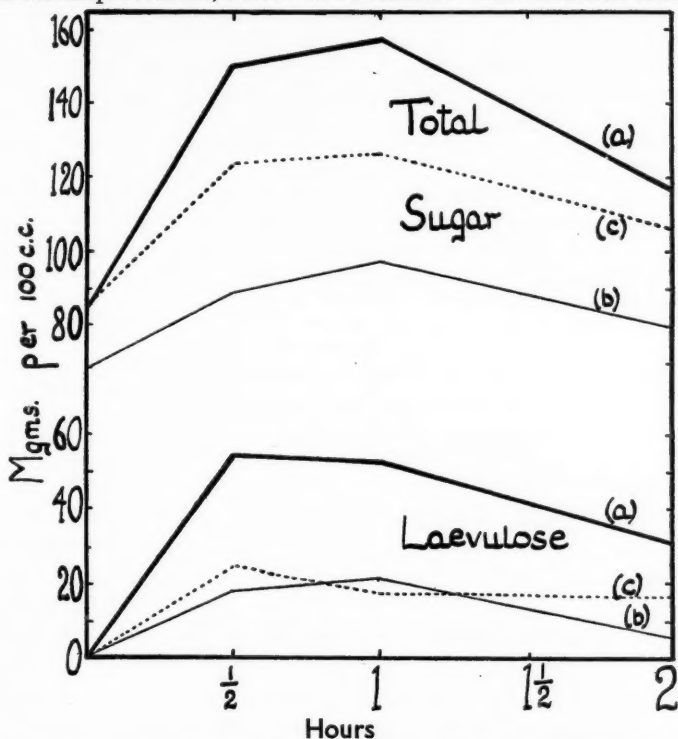


FIG. 5. Case 97. (a) on admission—clinical condition bad; (b) after clinical improvement; (c) after relapse.

and spleen on clinical examination was as before, but the patient was afebrile and there was then no jaundice. It will be noted that the curve is still abnormal if interpreted on the basis of the laevulose figures (although not if considered on the basis of total sugar estimations), but shows a marked improvement on the previous curve consistent with the improved clinical condition. Curve *c* was obtained nine weeks after curve *b*, the clinical picture, meanwhile, having shown no change. The close similarity between the two curves will be remarked.

*Case 124.* Male. Aged 6. Intermittent epistaxis for several years. Haematemesis before admission. No jaundice. Liver  $2\frac{1}{2}$  inches enlarged. Smooth and not tender. Spleen projects  $2\frac{1}{2}$  inches below costal margin; hard, regular, and tender. Red blood cells 3,800,000 per c.mm., Hb. 45 per cent. Colour index 0.6. *Diagnosis:* Gaucher's disease.

Gaucher's disease, properly so-called, is probably a variety of reticulo-endotheliosis and, as such, is not characterized pathologically by the series of changes to be seen in true splenic anaemia. It will be seen, however, that the response to the laevulose tolerance test in this case is closely similar to that obtained in the two previous cases. True, hepato-lienal fibrosis does

occur in the first decade of life (McMichael, 1934) and it is reasonable to suggest that this is the true diagnosis of the case outlined above.

*Case 25.* Female. Aged 52. Swelling of abdomen with abdominal pain and dyspnoea on exertion for three months. No enlargement of liver or spleen. No jaundice. Marked ascites. No evidence of renal disease. Wassermann: negative. After the abdomen had been tapped the spleen was felt just below the costal margin. Red cells 4,750,000. Hb. 83 per cent. per c.mm. Colour index 0.86. *Diagnosis:* Banti's disease.

In this case the diagnosis rests upon somewhat flimsy clinical evidence. The results of the laevulose tolerance test are normal in every respect and we accordingly question the diagnosis. From a consideration of the results of the laevulose tolerance test in hepato-lienal fibrosis we consider that this is a valuable method by which to investigate such cases as a means of assessing the amount of liver damage present. It is too soon, however, to use the test as a means of differentiating true hepato-lienal fibrosis from other hepato-splenomegalies.

10. *Carcinoma of the liver (primary or secondary).* Twelve cases of carcinoma of the liver were investigated and the results are shown in Table XII. Only four show normal laevulose values—cases 35, 51, 67, and 94—and of these four, case 94 is abnormal if interpreted on the basis of total sugar figures, and the diagnosis in cases 35 and 51 is doubtful. Case 67 shows several peculiar features, and the diagnosis of primary carcinoma of the liver must be accepted with reserve. The laevulose tolerance test was carried out three times (curve *b* being obtained two weeks after curve *a*, and curve *c* six weeks later). On each occasion the laevulose curve was well within normal limits. Indeed, the maximum laevulose value on any occasion never exceeded 6 mg. per 100 c.c., and the laevulose tolerance appears to have been better than normal. The total sugar curve in *b* is abnormal, however, and the glucose curve rises on each occasion. It is, of course, possible that in cases of early carcinoma, only localized areas of liver damage are produced and the remaining tissue functions normally, but such an explanation is hardly sufficient to account for these peculiarities. Case 80 is also of special interest. The clinical diagnosis was carcinoma of the liver—either primary or secondary—but no primary focus was found in spite of complete radiological investigation of the alimentary tract and thorough clinical examination. Our investigations suggest carcinoma of the pancreas. The high fasting blood-sugar is associated with a subsequent rise in the total blood-sugar values well above the maximum allowable and a marked rise in the blood-glucose. We might suggest also that the liver is the seat of metastases since the laevulose curve itself shows values in excess of normal. Case 82 affords an excellent example of the necessity for caution in interpreting the results of a laevulose tolerance test in arteriosclerotic patients. Whether one uses the actual laevulose figures or those for total sugar, there is evidently a tendency towards abnormal tolerance with arteriosclerosis. In this case, it appears likely that the decreased laevulose tolerance must have been due to the arteriosclerosis and not to liver disease.

*Case 1.* Male. Aged 40. Flatulence, heartburn, and abdominal discomfort for several years. Jaundice for nine months. Loss of weight. Liver four inches enlarged. Gall-bladder palpable. Icteric index 100. *Diagnosis:* carcinoma of pancreas; metastases in liver (autopsy).

*Case 35.* Female. Aged 70. Jaundice, asthenia, and anorexia for three weeks. Liver edge one inch above umbilicus. A smooth, hard, rounded tumour projects from it towards umbilicus. Wassermann: positive. Blood-pressure 150/70. *Diagnosis:* carcinoma of breast; metastases in liver (clinical evidence only; no later confirmation).

*Case 51.* Male. Aged 60. Oedema of feet and ankles and ascites for four weeks. Liver four inches enlarged, surface nodular, border irregular, firm and not tender. No jaundice. Wassermann: positive. Radial arteries calcified. Blood-pressure 220/60. *Diagnosis:* cardiovascular syphilis; carcinoma of liver, no primary focus found (clinical evidence).

*Case 67.* Female. Aged 32. Pain in the back for three months. Swelling of abdomen for three weeks. No jaundice. A hard, tender mass projecting from below the costal margin is continuous with a large mass in the flank. No ascites. Spleen normal. Blood-pressure 135/90. Curve *c* was obtained six weeks after curve *b* when patient's condition had deteriorated. Tumour diminished slightly in size on X-ray treatment. *Diagnosis:* ? primary carcinoma of liver (clinical evidence).

*Case 72.* Male. Aged 49. Pain in upper abdomen and loss of weight for six months. Jaundice for two weeks. Liver not generally enlarged. A mass projects from it below costal margin. Icteric index 36. Wassermann: negative. *Diagnosis:* carcinoma of liver, no primary focus found (clinical evidence).

*Case 76.* Male. Aged 59. Pain in right hypochondrium and loss of weight for twelve months. Palpable mass projects from liver two inches below costal margin. Icteric index 67. Wassermann: negative. *Diagnosis:* carcinoma of liver, no primary focus found (clinical evidence).

*Case 80.* Male. Aged 66. Epigastric pain, jaundice, and loss of weight for six months. Liver within half an inch of umbilicus, nodular, with irregular edge. Very firm and tender. Icteric index 178. *Diagnosis:* carcinoma of liver, no primary focus found (clinical evidence).

*Case 82.* Male. Aged 63. Constipation, abdominal pain, blood in stools for fourteen days. No jaundice. Radial arteries thickened. Blood-pressure 185/110. *Diagnosis:* carcinoma of pelvic colon; arteriosclerosis. No metastases found in liver at operation.

*Case 83.* Female. Aged 28. Abdominal pain and swelling for two months. Liver two inches enlarged, hard, irregular, and tender. Icteric index 16. *Diagnosis:* primary carcinoma of liver (autopsy).

*Case 92.* Female. Aged 40. Loss of weight for six months. Two attacks of diarrhoea in last four weeks. Hard swelling in right upper abdomen. No jaundice. Liver enlarged to umbilicus by a swelling arising from right lobe, smooth, and very hard. No ascites. *Diagnosis:* carcinoma of colon (hepatic flexure); metastases in liver (radiological). Evidence of metastases purely clinical, but supported by laevulose tolerance test (Fig 6).

*Case 94.* Male. Aged 57. Jaundice for six weeks. Abdominal swelling and loss of weight for one month. Liver one and a half inches enlarged, firm, smooth, and not tender. Icteric index 36. *Diagnosis:* primary carcinoma of liver (autopsy).

*Case 105.* Male. Aged 63. Pain in upper abdomen for six months. Loss of weight. Irregular, hard mass three and a half inches below costal margin.

No jaundice. Secondary anaemia. Blood pressure 125/67. *Diagnosis:* carcinoma of hepatic flexure; metastases in liver (operation).

11. *Liver dysfunction in diabetic patients.* The results of four cases of liver dysfunction in diabetic patients are shown in Table XIII. Cases 43 and 85 had

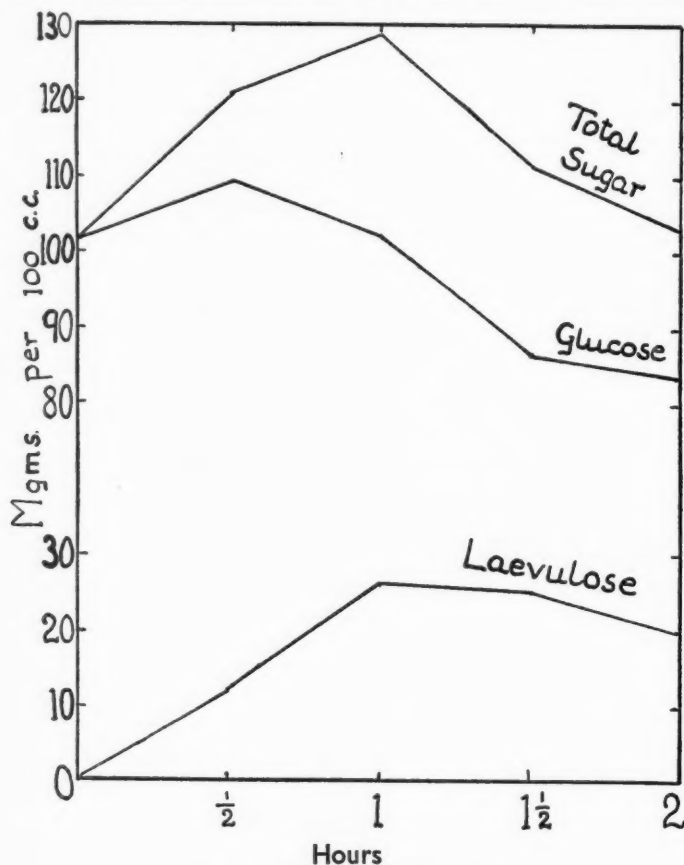


FIG. 6. Case 92. Carcinoma of liver.

obstructive jaundice and have already been described. In case 55 there was a prolonged history of alcoholism, and although there was no clinical evidence of hepatic disease, the laevulose test shows disturbance of hepatic function. In two of the four cases the laevulose curve rises well above the normal limits, while in all of them the total sugar curve, as in the cases of uncomplicated diabetes in Table IV, rises to very high levels. Although it is highly desirable that a large number of such cases should be investigated, it can nevertheless be seen that the laevulose tolerance test in its new form can now be applied to cases of hepatic dysfunction complicated by diabetes.

*Case 55.* Female. Aged 56. Long alcoholic history. Diabetic symptoms for six months. Stable on Cals. 1660; carbohydrate 71 gm. Urinary infection. *Diagnosis:* ? hepatic cirrhosis.

*Case 115.* Male. Aged 41. 'Moderate' spirit drinker. Abdominal pain and jaundice for fourteen days. Frequent 'bilious attacks'. Liver three inches enlarged, firm, regular, and tender. Icteric index 35. Van den Bergh test—biphasic. Glycosuria. Diabetic curve on glucose tolerance test. Stable on Cals. 2000; carbohydrate 157 gm. Insulin 15–10. *Diagnosis:* catarrhal jaundice; diabetes mellitus.

12. *Arteriosclerosis.* Table XIV shows the results obtained in five cases of arteriosclerosis. In four of these impaired laevulose tolerance is found, although there was no direct evidence of hepatic involvement. All the cases, except one, were over 60 years of age, and in four of the five the glucose curve shows a definite rise. Case 88 is associated with high total sugar and glucose curves suggesting impairment of pancreatic function. This is confirmed by clinical evidence of diabetes. In view of our findings, it would seem advisable that the results of the laevulose tolerance test in elderly arteriosclerotic individuals should be accepted with caution.

*Case 88.* Male. Aged 65. Thirst and polyuria for five months. Aching pain in left heel for six weeks. Glycosuria. Stable on Cals. 1919; carbohydrate 90 gm. Insulin 10–15–15. Radial arteries markedly thickened. Blood-pressure 145/75. *Diagnosis:* arteriosclerosis; dry gangrene.

*Case 89.* Male. Aged 69. Attacks of severe praecordial pain for two weeks. Exertion dyspnoea. Radial arteries thickened. Blood-pressure 140/110. No glycosuria. Wassermann: negative. *Diagnosis:* arteriosclerosis; angina pectoris.

*Case 99.* Male. Aged 60. Intermittent claudication for five years. Severe pain in right foot for one week. Radial arteries thickened. Blood-pressure 150/98. Wassermann: negative. No glycosuria. *Diagnosis:* arteriosclerosis; dry gangrene.

*Case 120.* Male. Aged 70. Radial arteries thickened. Blood-pressure 150/110.

*Case 125.* Male. Aged 46. Anginoid pain for five weeks. No dyspnoea or oedema. Flatulent dyspepsia. No jaundice. Liver normal. Arteries thickened. Blood-pressure 234/114. *Diagnosis:* malignant hypertension; angina pectoris.

The results from a miscellaneous selection of cases are shown in Table XV. The following are brief clinical notes:—

*Case 8.* Male. Grossly enlarged liver. No jaundice. *Diagnosis:* lymph-adenoma.

*Case 22.* Female. Aged 27. Incipient tuberculosis of left lung four years ago. Diabetes mellitus for four years. At the time of test patient was stabilized on Cals. 2800 and insulin 17–17. Slight fullness of thyroid. Skin flushed, warm, and moist. Slight exophthalmos. Moderate tremor. Blood-pressure 150/40. B.M.R. = +48 per cent. Curve *a* obtained. Thyroidectomy was performed and curve *b* was obtained two months later when the toxic symptoms had almost disappeared.

*Case 27.* Female. Aged 27. *Diagnosis:* acromegaly.

*Case 31.* Female. Aged 39. Dyspnoea on exertion and palpitation for sixteen months. B.M.R. = +20 per cent. Blood-pressure 150/72. Arteries not thickened. *Diagnosis:* toxic goitre.

*Case 57.* Female. Aged 65. *Diagnosis:* carcinoma of right kidney.

*Case 73.* Female. Aged 40. *Diagnosis:* tuberculous peritonitis.

*Case 114.* Female. Aged 27. *Diagnosis:* anorexia nervosa.

*Case 126.* Female. Aged 52. *Diagnosis:* carcinoma of stomach.

In case 22, curve *a* was obtained before, and curve *b* two months after thyroidectomy. The normal laevulose curve in *b* and the exceptionally high values for laevulose in curve *a* are interesting in view of the work of Cameron and Karunaratne (1935) and Youmans and Warfield (1926) on degenerative changes in the liver in thyrotoxicosis. Similar changes have also been reported by Gorodetski and Schesterikova (1937). In our only other case of thyrotoxicosis (case 31), however, the laevulose curve is normal. The response to the laevulose tolerance test in hyperthyroidism and other endocrine disorders is at present under investigation.

#### *Discussion*

The facts that ingestion of laevulose is usually followed by a variable decrease in blood-glucose and that this decrease is sometimes replaced by an increase, make it obvious that a laevulose tolerance test cannot possibly be satisfactory unless it is made to depend on estimations of laevulose itself. The ideal functional test would give a 'positive' result in every case of functional damage to the organ tested, and in no other cases, but in practice this ideal is never attained. Nevertheless, properly used, many function tests are of considerable value. They must, however, give positive results in a large proportion of cases in which functional deficiency exists; if they are liable to give positive results in other cases, the circumstances must be known in which these fallacious results may occur, and they must be sufficiently few not to interfere seriously with the usefulness of the test. In the absence of known sources of fallacy, the test must be so reliable that a positive result may be regarded as indicating functional damage even in the absence of satisfactory clinical evidence, and it is desirable, for prognostic purposes, that the degree of abnormality shown by the test should bear some relation to the amount of insufficiency. In very few cases, however, is it possible to use a function test in the converse manner, and to regard a normal result as indicating absence of damage. If these criteria are applied to the laevulose tolerance test, we believe that it emerges satisfactorily enough to make its extended use desirable.

In a series of 30 normal cases, covering the whole of adult life, we have found only a small range of variability in the laevulose tolerance test, hence there is reasonable certainty in classifying a given result as normal or abnormal. Non-hepatic disturbances of carbohydrate metabolism, such as diabetes, nervous disorders, &c., might conceivably have interfered with the laevulose

tolerance test and, indeed, did interfere with the test in its older form. In eleven such cases, however, the new test gave perfectly normal results, whereas the older form gave nine abnormal results, many of them grossly so. In seven other cases, not expected on clinical grounds to show liver deficiency, the new test was uniformly normal, although the older form gave three abnormal results. The new laevulose tolerance test can thus be used with safety in the presence of such non-hepatic disturbances of carbohydrate metabolism. It does, however, give 'positive' results in many cases of arteriosclerosis not associated with liver damage. In such cases, therefore, it must be interpreted with caution, as must the older form of the test, and, of course, the glucose tolerance test. Of 59 cases in which liver damage was known to exist, or in which there were reasonable clinical grounds for suspecting its existence, the laevulose tolerance test gave positive results in 45, and border-line results in two more—a reasonably high proportion. In certain cases, in which there existed the possibility of liver damage, but no adequate evidence of its existence at the time the laevulose tolerance test was done, the positive result of the test was confirmed later. Similarly, diagnoses of possible liver damage, based on rather inadequate clinical evidence and negatived by the laevulose tolerance test, have later had to be revised in the direction indicated by the test. This, however, is to be regarded as exceptional, for, as has been pointed out, a normal result in any function test ought not to be held as necessarily indicating normal functional capacity. In more than one case the test has been repeated at intervals, and the extent to which the result was abnormal has been found to parallel the clinical course of the patient. Our experience with the test has shown us that with its aid we may be able to attack several problems of interest, such as the significance of the 'lag' type of curve in the glucose tolerance test, the abnormalities of carbohydrate metabolism associated with arteriosclerosis, and the incidence of liver damage in thyrotoxicosis. In addition, it seems capable of yielding further information as to the site and route of laevulose break-down in the body. These problems are at present receiving attention, and we hope to publish results bearing on them in due course.

#### *Summary*

1. A modified form of the laevulose tolerance test of liver function is described. After ingestion of 50 gm. of laevulose, the blood-laevulose is estimated at half-hourly intervals for two hours.
2. Normally (30 cases) the blood-laevulose reaches a maximum, below 20 mg. per 100 c.c. within the first hour, and falls below 8 mg. per 100 c.c. at the end of two hours.
3. Abnormal results (i.e. a maximum above 20 mg. per 100 c.c.) were obtained in 45 out of 59 cases suspected, on adequate clinical grounds, of liver damage; two cases gave doubtful results.
4. Diabetes does not interfere with the test; arteriosclerosis does.

5. In a few cases, repetition of the test showed a parallelism between the clinical condition and the extent to which the laevulose curve was abnormal.

6. The results of 130 laevulose tolerance tests are reported. The cases are classified according to clinical condition, and the various classes are discussed individually.

It is a pleasant duty to thank the various members of the hospital staff, especially Prof. D. M. Dunlop, who have helped us by putting cases and case records at our disposal; Mr. J. D. Whittaker, the senior biochemical technician of this laboratory, for the estimations of total sugar quoted in this paper; and Dr. J. M. Munro, late junior biochemist, for making some of the laevulose determinations. We have also to acknowledge, with gratitude, a grant from the Moray Research Fund of Edinburgh University, which covered part of the expenses. (Dr. C. P. Stewart is in receipt of a part-time grant from the Medical Research Council.)

TABLE I

Mg. per 100 c.c. blood.

Case.	Total sugar.					Laevulose.					Glucose.				
	Hours after ingestion.					Hours after ingestion.					Hours after ingestion.				
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
3	82	93	84	81	80	0	12	13	10	5	82	81	71	71	75
4	93	102	92	90	89	0	8.5	10	12.5	4	93	93.5	82	77.5	85
6	82	91	84	82	80	0	14	10	8.5	3	82	77	74	73.5	77
7	90	92	85	83	82	0	18	13	7	4	90	74	72	76	78
10	99	108	100	98	98	0	16	14	12	3	99	92	86	86	95
11	90	94	92	90	90	0	15	14	11	5	90	79	78	79	85
12	90	102	96	90	90	0	14	11	8	4	90	88	85	82	86
13	94	96	90	89	89	0	10	16	10	8	94	86	74	79	82
29	88	97	93	89	87	0	14	13	8	4	88	83	80	81	83
30	82	90	85	81	81	0	10	7	4	1	82	80	78	77	80
32	100	100	102	99	100	0	9	11	9	8	100	91	91	90	92
36	100	109	106	102	98	0	10	6	4	1	100	99	100	98	97
40	90	96	92	90	90	0	15	11	3	1	90	81	81	87	89
41	88	93	90	89	88	0	8	10	10	2	88	85	80	79	86
44	110	122	115	—	109	0	10	8	—	11	110	112	107	—	98
47	92	101	95	—	91	0	15	14	—	7	92	86	81	—	84
50	85	89	86	84	84	0	6	13	6	4	85	83	73	78	80
64	93	98	101	93	90	0	4	7	8	4	93	94	94	85	86
100	88	98	92	—	89	0	13	9	—	2	88	85	83	—	87
127	80	95	96	84	79	0	10	12	4	2	80	85	84	80	77

TABLE I.  
Normal subjects  
(under 40 years)

TABLES II-IV

Mg. per 100 c.c. blood.

Case.	Total sugar.					Laevulose.					Glucose.				
	Hours after ingestion.					Hours after ingestion.					Hours after ingestion.				
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
59	83	90	101	92	84	0	7	10	8	4	83	83	91	84	80
61	86	100	92	87	84	0	5	5	4	3	86	95	87	83	81
63	90	138	121	115	110	0	23	16	15	16	90	115	105	100	94
117	82	104	86	86	82	0	5	10	10	11	82	99	76	76	71
118	79	82	82	83	86	0	6	7	9	7	79	76	75	74	79
119	95	112	123	—	117	0	12	10	—	3	95	100	113	—	114
121	82	95	104	—	105	0	11	10	—	10	82	84	94	—	95
122	75	100	84	—	82	0	10	7.5	—	11	75	90	76.5	—	71
128	79	107	107	—	99	0	12	11	—	3	79	95	96	—	96
129	77	82	90	—	86	0	11	5	—	6	77	71	85	—	80
9	90	122	103	66	91	0	14	9	6.5	2.5	90	108	94	89.5	88.5
39	104	115	109	—	106	0	9	10	—	4	104	106	99	—	102
84	90	104	96	—	88	0	11	14	—	5	90	93	82	—	83
16	112	148	130	114	111	0	11	10	9	10	112	137	120	105	101
18	182	259	298	307	324	0	16.5	14	8	21.5	182	252.5	284	299	302.5
24	171	205	186	180	175	0	16	15	16	10	171	189	171	164	165
34	193	216	237	264	227	0	7	8	10	5	193	209	229	254	218
60	193	264	325	338	286	0	13	13	21	12	193	251	312	317	274
132	167	190	209	—	201	0	7.5	14.5	—	15	167	182.5	194.5	—	186
133	163	245	224	—	216	0	8	10.5	—	7	163	237	213.5	—	209
135	136	203	233	—	171	0	11	16	—	5.5	135	192	217	—	165.5
136	390	419	451	—	499	0	13.5	17.5	—	12	390	405.5	433.5	—	487
109	89	102	97	94	88	0	26	17	17	11	89	76	80	77	77

TABLE IV.  
Diabetes  
mellitus

Glycosuria

## TABLES V-VIII

Mg. per 100 c.c. blood.

	Case.	Total sugar.					Laevulose.					Glucose.				
		Hours after ingestion.					Hours after ingestion.					Hours after ingestion.				
		0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
TABLE V. <i>Cardiac failure</i>	14	114	139	129	119	117	0	20.5	14	12	13	114	118.5	115	107	104
	15	95	109	121	143	121	0	10	21	19.5	9	95	99	100	123.5	112
	19	104	122	109	105	102	0	6.5	19	10	14	104	115.5	90	95	88
	20	129	136	130	128	128	0	6	13	8	8	129	130	117	120	120
TABLE VI. <i>Toxic jaundice</i>	5a	100	116	129	118	104	0	10	24	17.5	10	100	106	105	100.5	94
	5b	86	98	91	89	88	0	18	17	12	8	86	80	74	77	80
	28	99	111	118	120	105	0	7	11	10	9	99	104	107	110	96
	95a	86	100	92	87	84	0	5	5	4	3	86	95	87	83	81
TABLE VII. <i>Catarrhal jaundice</i>	95b	99	129	139	—	130	0	28	34	—	27	99	101	105	—	103
	123	92	119	134	—	110	0	14	28	—	10	92	105	106	—	100
	17	100	130	146	146	139	0	26	22	18	20	100	104	124	128	114
	33	105	109	119	110	107	0	12	18	9	6	105	97	101	101	101
TABLE VIII. <i>Obstructive jaundice</i>	62	80	105	111	96	84	0	15	9	6	4	80	90	102	90	80
	75	92	161	130	—	99	0	13	13	—	11	92	148	117	—	88
	78	95	116	124	—	131	0	30	37	—	15	95	86	87	—	116
	79	82	107	145	—	138	0	14	20	—	14	82	83	125	—	124
TABLE IX. <i>Cirrhosis</i>	103	91	119	110	—	94	0	27	23	—	15	91	92	87	—	79
	110	90	104	97	—	89	0	22	7	—	6	90	82	90	—	83
	26	100	128	119	—	109	0	3	6	—	3	100	125	113	—	106
	42	98	123	140	—	110	0	10	12	—	5	98	113	128	—	105
TABLE X. <i>Diabetes</i>	43	106	129	183	—	246	0	13	15	—	13	106	116	168	—	233
	46a	98	119	128	140	127	0	26	34	47	38	98	93	94	93	89
	46b	70	134	120	90	78	0	14	18	—	16	70	120	102	—	62
	52	86	99	123	109	94	0	19	23	30	15	86	80	100	79	79
TABLE XI. <i>Arteriosclerosis</i>	69	80	124	103	—	93	0	26	26	—	16	80	98	77	—	77
	74	90	156	142	—	122	0	12	37	—	13	90	144	105	—	109
	81	108	120	110	107	107	0	20	52	47	108	100	90	55	60	60
	85	210	255	321	—	289	0	36	38	—	16	210	219	283	—	273
TABLE XII. <i>Miscellaneous</i>	86	85	114	108	—	102	0	12	16	—	11	85	102	92	—	91
	87	111	139	159	147	140	0	35	34	32	27	111	104	125	115	113
	104	115	159	167	—	129	0	49	38	—	21	115	110	129	—	108
	134	112	138	166	—	132	0	13	21	—	18	112	115	145	—	114

## TABLES IX-XI

Mg. per 100 c.c. blood.

	Case.	Total sugar.					Laevulose.					Glucose.				
		Hours after ingestion.					Hours after ingestion.					Hours after ingestion.				
		0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
TABLE IX. <i>Cirrhosis</i>	21	97	120	140	176	145	0	19	54	37	35	97	101	86	139	110
	37	96	105	96	—	88	0	18	23	—	15	96	87	73	—	73
	45	84	112	106	93	85	0	8	24	28	32	84	104	82	65	53
	48	93	101	96	—	92	0	15	13	—	8	93	86	83	—	84
TABLE X. <i>Diabetes</i>	54	92	100	108	99	93	0	15	22	22	25	92	85	86	77	68
	56	86	99	117	102	92	0	16	11	9	16	86	83	106	93	76
	58	89	96	109	—	—	0	10	16	—	—	89	86	93	—	—
	65	90	139	120	—	109	0	9	13	—	14	90	130	107	—	95
TABLE XI. <i>Arteriosclerosis</i>	66	80	127	115	—	99	0	11	8	—	3	80	116	107	—	96
	68	82	114	131	114	84	0	16	29	22	11	82	98	102	92	73
	70a	79	93	121	—	135	0	9	13	—	25	79	84	108	—	110
	70b	94	142	135	—	114	0	25	32	—	12	94	117	103	—	102

TABLES IX-XI (*continued*)

Mg. per. 100 c.c. blood.

		Total sugar.					Laevulose.					Glucose.				
		Hours after ingestion.					Hours after ingestion.					Hours after ingestion.				
		0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
TABLE IX (continued)	Case.	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2
	90	80	90	96	—	89	0	23	25	—	10	80	67	71	—	79
	106	82	107	136	119	96	0	35	55	26	11	89	72	101	93	85
	112	89	114	103	—	96	0	15	21	—	4	89	99	82	—	92
	113	106	120	151	131	109	0	29	39	22	10	106	91	112	109	99
	130	104	119	139	—	112	0	14	36	—	16	104	105	103	—	96
TABLE X. <i>Syphilitic cirrhosis</i>	38	101	130	141	133	115	0	22	23	12	9	110	108	118	121	106
	91	101	108	117	—	125	0	17	18	—	10	101	91	99	—	115
	25	102	112	108	104	103	0	6	6	10	5	102	106	102	94	98
TABLE XI. <i>Hepato-lineal fibrosis.</i>	96	109	155	175	—	132	0	43	43	—	17	109	112	132	—	115
	97 a	86	150	158	—	117	0	55	53	—	31	86	95	105	—	76
	97 b	70	88	97	—	79	0	17.5	22	—	5	70	70.5	75	—	74
	97 c	86	123	126	—	107	0	24	17.5	—	16	86	99	108.5	—	91
	124	84	123	152	—	110	0	30	55.5	—	41	84	98	96.5	—	69

## TABLES XII-XV

Mg. per 100 c.c. blood.

Case.	Total sugar.					Laevulose.					Glucose.					
	Hours after ingestion.					Hours after ingestion.					Hours after ingestion.					
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	
1	90	102	122	99	90	0	32.5	37.5	16	2.5	90	69.5	84.5	83	87.5	
35	120	140	142	139	150	0	12	12	10	14	120	128	130	129	136	
51	81	86	80	—	79	0	6	10	—	5	81	80	70	—	74	
67 a	82	110	95	—	84	0	6	3	—	2	82	104	92	—	82	
67 b	90	128	105	—	93	0	4	5	—	2	90	124	100	—	91	
67 c	90	101	94	—	87	0	5	5	—	4	90	96	89	—	83	
72	88	108	99	—	89	0	27	11	—	4	88	81	88	—	85	
76	104	153	120	—	99	0	35	28	—	5	104	118	92	—	94	
80	140	210	180	160	149	0	18	32	32	25	140	192	148	128	124	
82	88	102	119	110	101	0	16	31	25	18	88	86	88	85	83	
83	78	94	107	—	116	0	22	25	—	21	78	72	82	—	95	
92	102	121	128	111	103	0	12	26	25	20	102	109	102	86	83	
94	84	116	110	—	88	0	12	10	—	6	84	104	90	—	82	
105	96	114	114	—	105	0	24	31	—	24	96	90	83	—	81	
TABLE XIII. Diabetes and liver dys- function	43	106	129	183	—	246	0	13	15	—	13	106	116	168	—	233
	55	114	150	149	169	140	0	12	27	32	20	114	138	122	137	120
	85	210	255	321	—	289	0	36	38	—	16	210	219	283	—	273
	115	182	253	282	306	296	0	5.5	9	—	4.5	186	218.5	251	—	210.5
	88	119	130	166	—	148	0	10	17	—	20	119	120	149	—	128
TABLE XIV. Arterio- sclerosis	89	88	104	98	—	86	0	26	28	—	13	88	78	70	—	73
	99	75	129	141	—	—	0	26	28	—	—	75	103	113	—	—
	120	153	162	175	—	159	0	6	9	—	10	153	156	166	—	149
	125	88	122	106	—	84	0	24	16	—	4	88	98	90	—	80
	8	90	127	110	98	94	0	25	13	11	7.5	90	102	97	87	86.5
22 a	290	340	429	387	322	0	54	116	80	75	290	286	313	307	247	
22 b	129	165	160	—	151	0	20	11	—	9	129	145	149	—	142	
27	92	101	97	95	93	0	8	11	2	4	92	93	86	93	89	
31	106	135	112	108	104	0	10	7	4	3	106	125	105	104	101	
57	84	91	101	—	100	0	16	17	—	18	84	75	84	—	82	
73	93	105	121	—	98	0	6	12	—	10	93	99	109	—	88	
114	99	111	125	120	102	0	5	9	14	6	99	106	116	106	96	
126	102	148	158	158	124	0	12	18	16	4	102	136	140	142	120	
TABLE XV. Miscellaneous																

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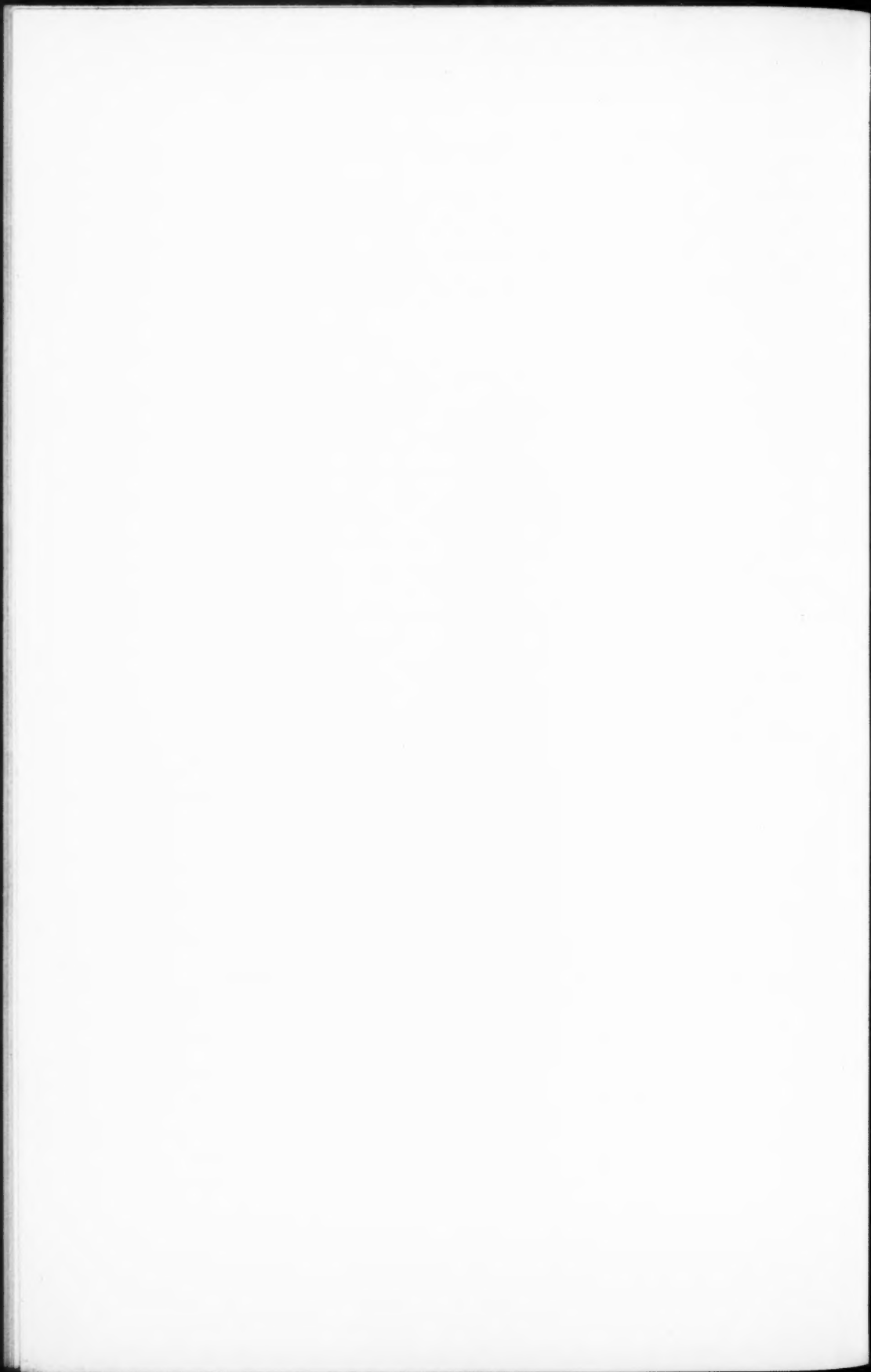
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## TUBERCULOUS SPLENOMEGALY, WITH MILIARY TUBERCULOSIS OF THE LUNGS<sup>1</sup>

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(From Charing Cross Hospital)

With Plates 19 and 20

HOYLE and Vaizey (1937), in their monograph 'Chronic Miliary Tuberculosis', state that by far the most frequent evidence of haematogenous dissemination of tuberculosis, elsewhere than in the lungs, is enlargement of the spleen. This enlargement was present in 31 of the 120 cases of chronic miliary tuberculosis which they review; it was usually slight or moderate, but in three cases of the series it was so great that it required splenectomy to relieve symptoms (the cases reported by Bjerring, 1927; Cohn, 1925; Klingenstein, 1926). In the two cases described below, tuberculous splenomegaly was accompanied by radiological evidence of miliary tuberculosis of the lungs. In both cases the radiological signs of miliary tuberculosis of the lungs disappeared following clinical cure effected by splenectomy.

### Cases

*Case 1.* Male, first seen in November 1934, at the age of 35. For three years he had noticed lack of energy, causing difficulty in carrying out his work as a postman and he had lost 2 stones in weight. He had had winter cough for four years, with very little sputum and no haemoptysis. The cough had always disappeared in the summer. There had been night sweats for two years. He had had frequent boils, and suffered from a gonorrhoeal stricture of the urethra. For three weeks before admission to hospital he had noticed enlargement of the inguinal lymph glands. Massive enlargement of the spleen was the most prominent sign (Fig. 1). The lung signs were consistent with a diagnosis of chronic bronchitis, and 12 sputum tests were negative for the tubercle bacillus. There was some enlargement of the inguinal glands, mainly on the left side, with no enlargement of the cervical or axillary glands. The patient was afebrile except for occasional rises of temperature up to 99° F. The urethral stricture required dilatation. Radiological examination of the lungs showed very extensive miliary shadows throughout both lungs (Plate 19, Fig. 2). Following this finding, an inguinal lymph gland was excised for histological examination, and this showed the typical changes of chronic tuberculosis. A chronic sero-purulent discharge developed from the wound, which persisted until after he left hospital.

*Blood examination.* Haemoglobin percentage, 100. Red blood cells, 5.18 million per c.mm. Leucocytes (counted three times before operation), 4,000 to 5,300 per c.mm. Neutrophil polymorphs, 67.5 to 75.5 per cent., lymphocytes, 13 to 17 per cent., monocytes, 10 to 11 per cent., eosinophils, 0 to 4 per cent., basophils, 0 to 1 per cent. No abnormal red or white cells were seen. Platelets (counted once), 410,000 per c.mm. Fragility of red blood cells, normal. Van

<sup>1</sup> Received December 17, 1937.

den Bergh reaction, direct, negative; indirect, very slightly above normal limits. Wassermann reaction, negative. Test meal analysis (without histamine), achlorhydria, except for the 2½ hour sample, which contained a small amount of free acid.

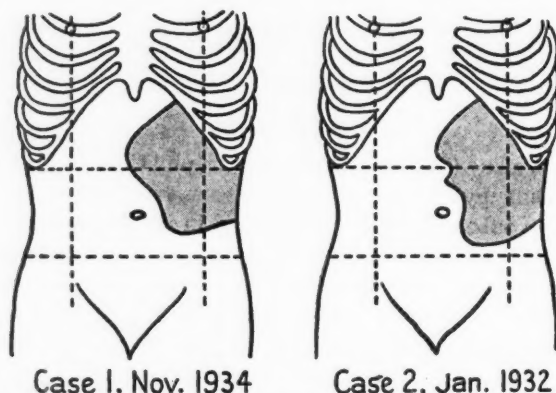


FIG. 1. Diagrams, from drawings made at the time of examination, to show the size of the spleen in the two cases.

Splenectomy was carried out in January 1935. At operation a great many enlarged lymph glands were found in the abdomen, but there was no naked eye evidence of liver involvement. The patient made an uninterrupted recovery, and three months after the operation he felt quite well, the glands in the groins had disappeared, he had regained the lost weight, and returned to work. Radiological examination of the lungs three months after the operation showed considerable reduction in the extent of the miliary shadows, and in January 1937, two years after splenectomy, the miliary shadows had practically disappeared (Plate 19, Fig. 3). In November 1937, two years and ten months after operation, he was in excellent health, and had had only one week away from work because of a mild attack of 'influenza' since the operation. Radiological examination of the lungs at this time showed no notable abnormality, except for changes suggesting early fibrosis of the right apex, and there was no clinical evidence of enlargement of lymphatic glands or liver. The blood was examined three times between the time of operation and November 1937. The total leucocyte count varied between 8,000 and 12,000 per c.mm. and the differential count showed: neutrophil polymorphs, 46.0 to 59.5 per cent., lymphocytes, 31.0 to 36.5 per cent., monocytes, 9.0 to 14.0 per cent., eosinophils, 0.0 to 6.0 per cent., basophils, 0.5 to 1.5 per cent. The splenic surface was slightly irregular, and of a yellowish-red colour. The cut surface presented a finely lobulated appearance, due to the presence of small yellowish-red areas, with fairly well-defined margins, which were crowded together so that there was no visible splenic tissue between them. Microscopically the splenic tissue was almost entirely replaced by tissue showing the histological features of tuberculosis, with typical focal arrangement, but without caseation. Here and there portions of a Malpighian body, and small portions of splenic pulp, could be seen. Tubercle bacilli were not demonstrated by staining methods.

*Case 2.* Female, first seen in June 1931, at the age of 34. For three months she had noticed abnormal tiredness and shortness of breath, and had had two

attacks, each lasting a few days, of very severe pain in the left upper abdomen. Her spleen was found to be greatly enlarged (see Fig. 1). There was slight anaemia (haemoglobin, 76 per cent.), and the leucocytes numbered 5,200 per c.mm., with a normal differential count. No enlarged lymph glands were present, and no other signs of disease were found. She was seen again in January 1932, having had five attacks of severe pain over the spleen. She was readmitted and investigated. The chief results of this investigation were: Haemoglobin percentage 65 to 70. Red blood cells, 4 million per c.mm. Leucocytes (counted four times before operation), 3,600 to 5,200 per c.mm. Neutrophil polymorphs, 58 to 74 per cent., lymphocytes, 10.5 to 21 per cent., monocytes, 12.5 to 22 per cent., eosinophils, 1.5 to 5 per cent., basophils, 0 to 1 per cent. No nucleated red cells or myelocytes were found. Platelets, 372,000 per c.mm. Fragility of red cells, normal. Van den Bergh reaction, direct, negative; indirect, not above normal limits. Wassermann reaction, negative. Test meal analysis (without histamine), normal. Radiological examination of long bones, no abnormality.

There were no symptoms or signs suggesting pulmonary disease, and no radiological examination of the chest was made at this time. No diagnosis was made, except for a tentative diagnosis of splenic anaemia, but splenectomy was deemed to be indicated, because of the severe pains over the spleen, each attack of which incapacitated the patient for several days. This was carried out in March 1932, a year after the onset of symptoms. At operation there were found large numbers of round reddish masses in the abdomen, which were thought to be either spleniculi or enlarged lymph glands, and the surface of the liver showed large numbers of yellow spots. No specimen of liver or lymph gland was removed for microscopical examination. The patient made an uninterrupted recovery from the operation, except for collapse of the left lung base for a few days, and after four weeks was back at her household duties. She was soon able to carry these out without undue fatigue, and stated that she felt 'quite different'. Radiological examination of the chest carried out nine months after splenectomy, when the patient had already felt quite well for several months, revealed extensive miliary shadows in both lungs, particularly the left (Plate 20, Fig. 4). This examination was repeated three and a half years after splenectomy, and showed that the miliary shadows had practically disappeared (Plate 20, Fig. 5). Had the chest been investigated radiologically before the operation, the discovery of the miliary shadows would have enabled the diagnosis of tuberculous splenomegaly to be made, as in Case 1. The patient was in good health in November 1937, five years and eight months after splenectomy; she had had no illness since the operation, and radiological examination of the chest revealed only very fine linear shadows suggesting early scattered fibrosis. The blood was examined seven times between the time of the operation and November 1937. The main findings were the disappearance of the anaemia, the total leucocyte count was between 8,200 and 11,000 per c.mm. and the differential leucocyte counts showed: neutrophil polymorphs, 45.0 to 66.5 per cent., lymphocytes, 12.5 to 34.5 per cent., monocytes, 10.5 to 16.5 per cent., eosinophils, 3.5 to 6.0 per cent., basophils, 0.5 to 2.5 per cent. The surface of the spleen presented a mottled appearance, due to the presence of small pink areas, lying close together. The cut surface was of a mottled pink and white colour, no normal spleen tissue being recognizable. Microscopically the spleen structure was almost entirely replaced by tissue showing the typical histological features of tuberculosis, without caseation, and tubercle bacilli were demonstrated by staining methods.

*Discussion*

There is insufficient evidence as to how frequently tuberculous splenomegaly is accompanied by chronic miliary tuberculosis of the lungs, for radiological examination of the lungs is not often recorded in such cases. The splenomegaly dominates the clinical picture, and pulmonary symptoms and signs may be entirely absent, as in Case 2. In the three cases of chronic miliary tuberculosis with tuberculous splenomegaly referred to by Hoyle and Vaizey (Bjering, 1927; Cohn, 1925; Klingenstein, 1926), the radiological signs of miliary tuberculosis of the lungs were discovered after the nature of the splenomegaly had been ascertained by examination of the excised spleens. It is therefore advisable to investigate the lungs radiologically in every case of splenomegaly of obscure nature, even in the absence of any pulmonary symptoms or signs, for this will occasionally reveal the presence of miliary tuberculosis of the lungs, and thus enable the nature of the splenomegaly to be ascertained. My two cases support the view of the majority of authors that the presence of tuberculous disease elsewhere is not a contra-indication to splenectomy in tuberculous splenomegaly, and that spontaneous cure of other tuberculous lesions may occur following the operation. In Case 1, besides tuberculosis of the spleen, there were present tuberculosis of the inguinal and intra-abdominal lymph glands, and miliary tuberculosis of the lungs; and in Case 2, apart from tuberculosis of the spleen and miliary tuberculosis of the lungs, there were present tuberculosis of the intra-abdominal lymph glands, and almost certainly also miliary tuberculosis of the liver. A few authors have held that the presence of tuberculous disease in other organs is a contra-indication to splenectomy (Locquette, 1928; Magnac, 1924). The rapid relief of symptoms, enabling the patients to resume their normal occupations within one month and three months of splenectomy, in spite of the evidence of disease elsewhere, suggests that splenectomy should be carefully considered in cases of chronic miliary tuberculosis with enlargement of the spleen, even if this is not great enough to produce local symptoms. The rapid return to health in these cases suggests the possibility that the effect of splenectomy may be due to some unknown factor in addition to the removal of a large mass of tuberculous disease in a non-essential and easily removable organ.

The diagnosis of tuberculous splenomegaly has seldom been made, in the recorded cases, prior to splenectomy or post-mortem examination. For example, it was not made once in the 50 cases collected from the literature by Winternitz, 1912; and only once in the 19 cases collected by Magnac, 1924 (in that of Kümmell, 1912). The diagnosis depends upon the recognition of active or healed tuberculous lesions in other organs, or a history of tuberculous disease earlier in life, in a patient with massive enlargement of the spleen (Greppi, 1933; Morawitz and Denecke, 1926; Quénu and Baudet, 1898). The diagnosis has been made, for example, on the following various features: a history of tuberculous glands in childhood and an active apical pulmonary lesion (Kümmell, 1912); tuberculous osteitis of radius (Villard and Santy, 1913);

a healed pulmonary lesion and a history of probable tuberculous peritonitis earlier in life (Giffin, 1919); tuberculous cervical lymphatic glands (Peck, 1924); pulmonary tuberculosis (Kellert, 1931; Tapie, 1926); Pott's disease of the spine and multiple tuberculous abscesses (Weil, Isch-Wall, and Perlès, 1936). It is doubtful if tuberculous splenomegaly ever occurs without tuberculous lesions elsewhere; of the 50 cases collected from the literature by Winternitz, 1912, it is stated that in only one case was the spleen alone affected. It is difficult to ascertain in what proportion of cases clinically recognizable tuberculous lesions occur, which would enable the correct diagnosis to be made, for in most cases the spleen was removed after a tentative diagnosis of splenic anaemia or Banti's disease, without special care having been taken to exclude active or healed tuberculosis, or a history of tuberculosis earlier in life, and in only a few are radiological examinations of the lungs recorded. The resemblance to splenic anaemia and Banti's disease is further suggested by the occasional occurrence of haematemesis (Bunch, 1931; Locquette, 1928) and ascites (Klingenstein, 1926; Price and Jardine, 1931). Methods of investigation accessory to clinical examination have not been found to be of value in making the diagnosis of tuberculous splenomegaly. Blood counts have given variable results (Hirschfeld, 1920; Winternitz, 1912) though a slight leucopenia with relative mononucleosis is most frequent (Léon-Kindberg, 1927). Polycythaemia may occur (Coyon, Clog, and Brun, 1927; Douglas and Eisenbrey, 1914; Weil, 1934; Rendu and Widai, 1899), though as more cases are recorded this is less common than was thought to be the case by earlier authors (Locquette, 1928). Occasionally myelocytes have been found in the blood, associated with myeloid metaplasia of the tuberculous spleen (Coyon, Clog, and Brun, 1927; Weil, 1934; Giffin, 1919; Hugonot and Sohier, 1935; Price and Jardine, 1931; Swirschewskaja, 1926), and there are differences of opinion as to whether these are cases of myelosis with complicating tuberculous disease, or whether the myeloid metaplasia is secondary to the tuberculosis of the spleen. Rarely the blood examination has shown thrombocytopenia, associated with purpura (Kellert, 1931). Tuberculin reactions and skin tests have proved disappointing, having given negative results in proved cases (Bjering, 1927; Greppi, 1933; Klingenstein, 1926; Locquette, 1928; Nassau, 1926). Splenic puncture has occasionally been recorded as giving positive results, the fluid withdrawn being found to contain tubercle bacilli, or to produce tuberculosis in guinea-pigs (Coyon, Clog, and Brun, 1927; Weil, Isch-Wall and Perlès, 1936; Nassau, 1926). But the result cannot be relied upon, as it depends on chance whether the puncturing needle enters a part of the spleen containing the organisms (Weil, Isch-Wall, and Perlès, 1936; Hirschfeld, 1920), and so a negative result may be obtained in a case afterwards proved to be one of tuberculous splenomegaly (Greppi, 1933). Levy (1932) described a case in which the spleen became one-third smaller after a subcutaneous injection of adrenalin, and this was followed by a rigor and rapid deterioration in the condition of the patient. He considered that this result was due to dissemination throughout the body of tubercle bacilli from the contracting spleen. He

therefore concluded that investigation of the contractibility of the spleen after subcutaneous injection of adrenalin was dangerous in cases of tuberculous splenomegaly, and that the result would not assist in distinguishing between cases of this disease and some other types of splenomegaly. In some cases radiological examination of the splenic region has revealed calcified areas, and this has suggested the diagnosis of tuberculous splenomegaly (Bunch, 1931; Courtin and Duken, 1928; Shands, 1933), but most tuberculous spleens removed at operation or examined *post mortem* have not contained any calcified areas, so that this investigation would rarely be of assistance.

### Summary

1. Two cases are described of tuberculous splenomegaly associated with the radiological appearances of miliary tuberculosis of the lungs.
2. In both cases complete relief of symptoms was produced by splenectomy, and the patients were in good health two years and ten months, and five years and eight months after operation.
3. The means by which the diagnosis of tuberculous splenomegaly is made are discussed.

Both patients were under the care of the writer in Charing Cross Hospital, the splenectomies were carried out by Mr. Norman Lake, and the spleens are in the Museum of Charing Cross Hospital Medical School.

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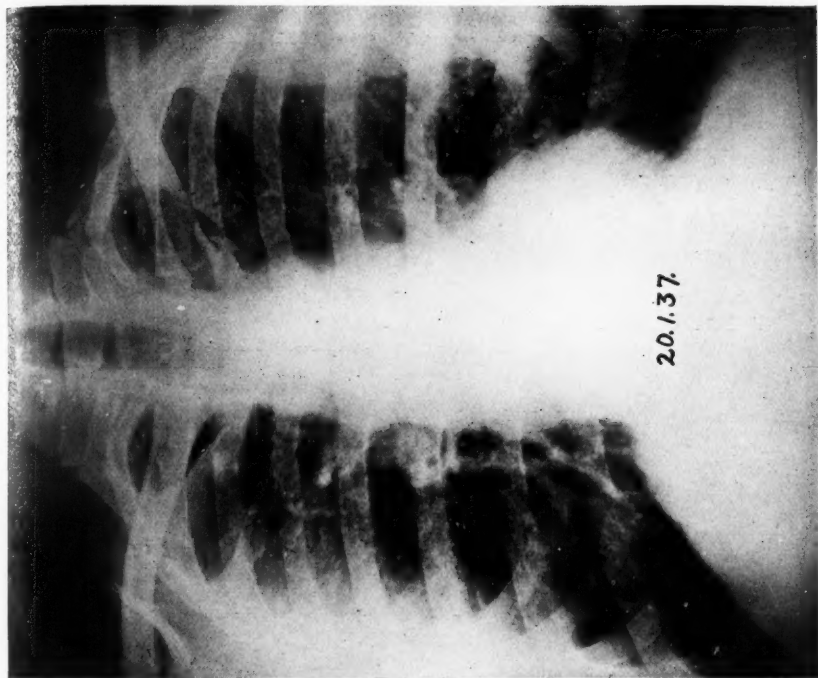


Fig. 3. Case 1. X-ray of chest two years after operation

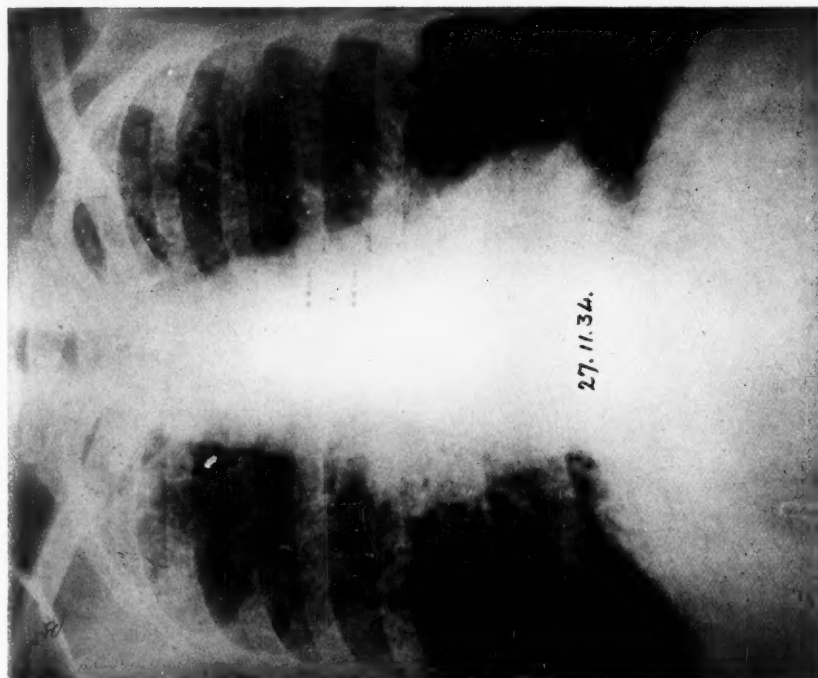


Fig. 2. Case 1. X-ray of chest before operation



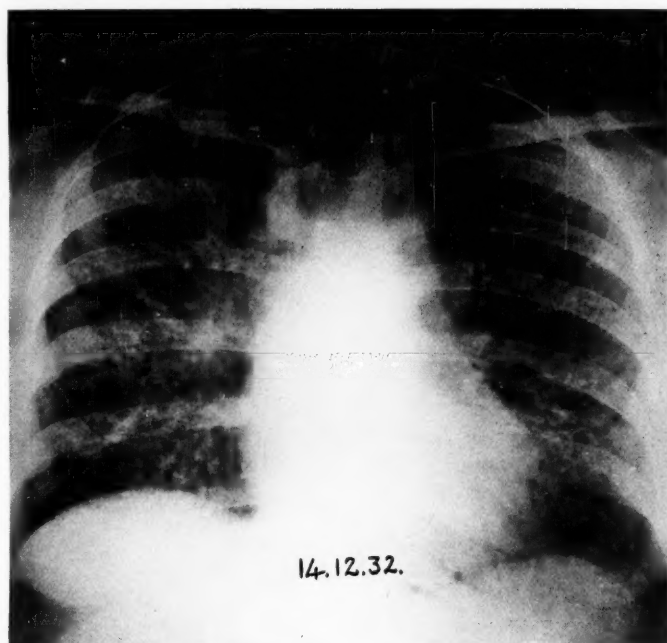


FIG. 4. Case 2. X-ray of chest nine months after operation

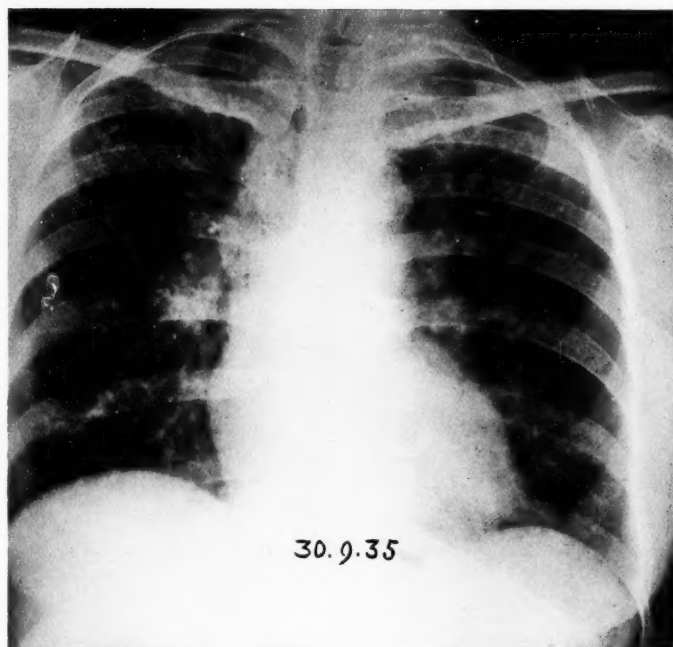
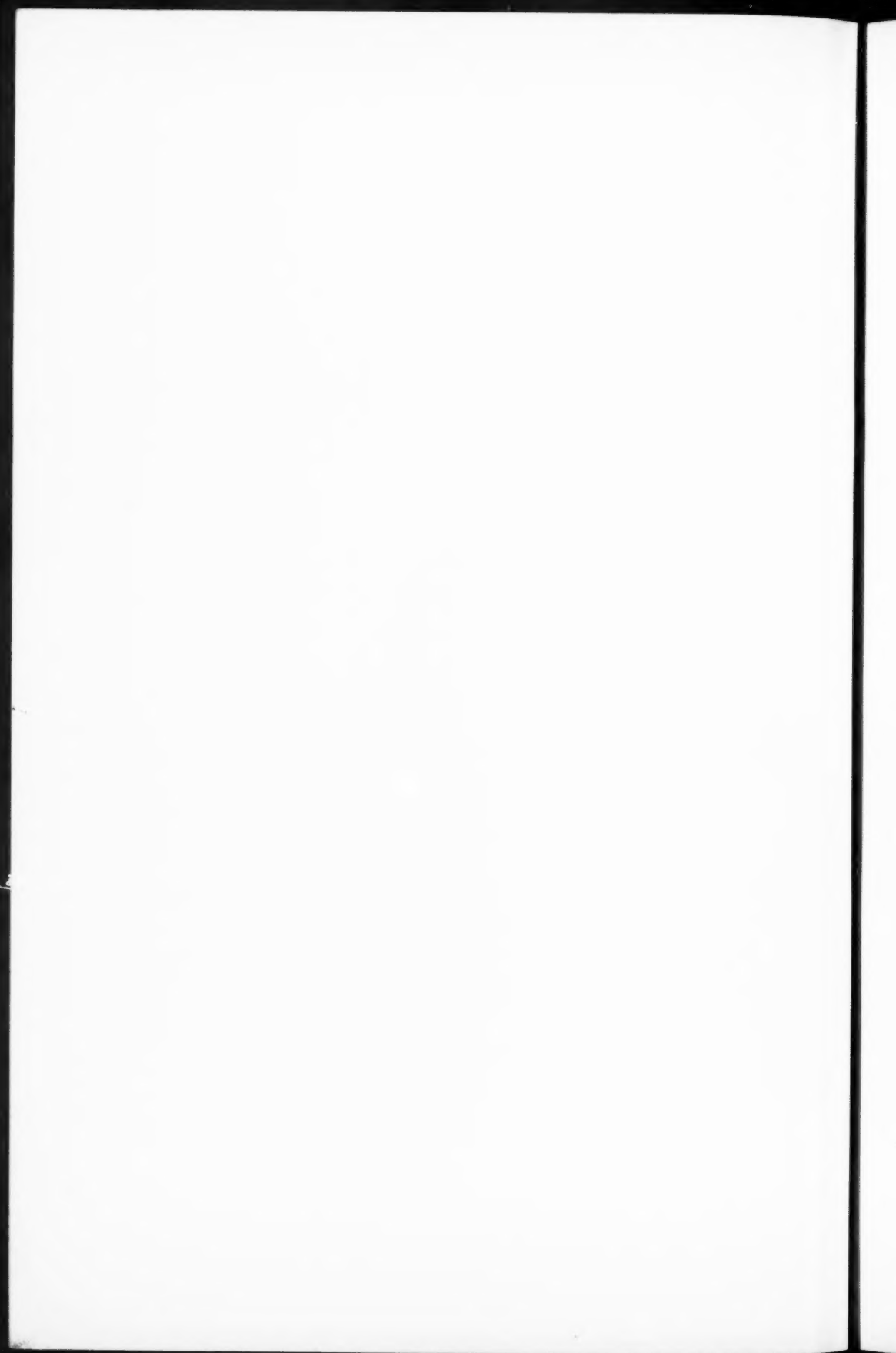


FIG. 5. Case 2. X-ray of chest three and a half years after operation



INSULIN ANTAGONISM<sup>1</sup>

BY ALEXANDER GLEN AND JAMES CAITHNESS EATON

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MANY cases in which insulin failed to lower the blood-sugar in the normal manner have been recorded since insulin first came to be used in the treatment of diabetes in 1923. One such case, found in the Diabetic Clinic of the Victoria Infirmary, Glasgow, was made the subject of considerable investigation. Though other patients have received larger doses of insulin within twenty-four hours than this patient ever received, none appears to have received such large doses for so prolonged a period; this patient received 900, and later 1,050 units daily during a period of twenty-seven days without appreciable effect on the blood-sugar or glycosuria.

*Case Report*

The patient was a married woman with six children alive and well. Her mother and a sister were diabetic. The clinical history of the disease in the mother is unknown, but the sister had responded well to moderate doses of insulin. The patient was of stout build, her weight averaging 64 to 70 kg. When she first attended hospital in 1928 she was 38 years of age and complained of uterine haemorrhage. Curettage was twice performed during 1928 without relief. In December 1928 a sub-total hysterectomy was performed and the right ovary removed. In December 1929 the patient returned, complaining of vague abdominal pain, and was admitted to hospital for observation. Adhesions were diagnosed as the cause of the pain. Glycosuria was discovered for the first time on routine examination on this occasion. On being questioned she admitted having had thirst, polyuria, weakness, and a burning sensation on micturition for some weeks previously. On 6.2.30 the patient was admitted for treatment. The urinary sugar was 4 per cent., no acetone was present, but there was a trace of albumin. Sugar tolerance test as in Fig. 1. Discharged on 23.3.30 feeling well, on a diet of 90 gm. carbohydrate, 67.5 gm. protein and 135 gm. fat, with 90 units of insulin daily. There was still, however, 1.75 per cent. of sugar in the urine. From this time until August 1933 she attended as an out-patient, receiving the above diet, but the insulin was gradually increased to 180 units daily, since glycosuria, thirst, and pruritus persisted, though there was practically no ketonuria. On 30.8.33 she was re-admitted to try and improve her condition. She was put on a diet of 80 gm. carbohydrate, 60 gm. protein, 120 gm. fat, with 195 units of insulin daily. The symptoms were allayed, but there was

<sup>1</sup> Received December 16, 1937.

still 0.8 per cent. urinary sugar on discharge on 19.9.33. She continued to attend as an out-patient until 31.7.34 when she was re-admitted to hospital complaining of pain in the left flank. The urinary sugar was 6 per cent. No local treatment was instituted. Diet was reduced to 70 gm. carbohydrate, 60 gm. protein, and 120 gm. fat, with 225 units of insulin daily. The condition improved, but she was still much troubled by pruritus. Discharged on 19.8.34 with urinary sugar still 2.5 per cent. In February 1936 the patient broke a hypodermic needle in her thigh and was admitted on 24.2.36 to have the needle removed. Diet 90 gm. carbohydrate, 67.5 gm. protein, and 135 gm. fat, with 270 units of insulin daily. The urinary sugar was 5 per cent. The sugar tolerance at this time is also shown in Fig. 1. As insulin appeared to have so little effect, none was given for two days, but marked ketosis rapidly developed and its administration had to be recommenced. Discharged on 16.3.36. On 20.4.36, at 7 a.m., she injected 400 units of insulin (quadruple strength) in one dose with intent to commit suicide on account of the intolerable pruritus. The only food taken after this dose was a cup of tea. She felt slight nausea, but did not vomit and there was slight pain at the heart, but no other symptoms. She remained in bed all day feeling heavy and sleepy and took very little food. On account of this her insulin was increased at once to 800 units daily in three doses of 200, 400, and 200 units each, but even so, her blood-sugar was found to be 438 mg. per 100 c.c. Now, for the first time, acetone began to appear in the urine in considerable quantities. On 18.5.36 she was admitted to hospital as an urgent case. The blood-sugar was 316 mg. per 100 c.c., urinary sugar 6 per cent., acetone + + +. It is possible that the appearance of acetone at this time may have been due to her failing to take her insulin regularly, as she complained greatly of the pain resulting from the frequent bulky injections necessary. During this stay in hospital the insulin dosage was increased to 900 units daily and after eight days to 1,050 units daily, which quantity she received for nineteen consecutive days, except on a few days when experimental work was being performed, the morning dose being modified on these occasions for the sake of the investigations. The diet was 100 gm. carbohydrate, 45 gm. protein, and 90 gm. fat. This régime was entirely without effect on the glycosuria. A considerable amount of investigation was carried out at this time as detailed below. On 19.6.36 the patient demanded to be allowed to go home contrary to advice, and on 22.6.36 she was re-admitted in diabetic coma. An exact history could not be obtained, but it appeared that she had had some domestic worries and had failed to take her diet. She had had 900 units of insulin daily. Vomiting commenced and she rapidly went into deep coma. On admission the urine was loaded with sugar, blood-sugar 1,239 mg. per 100 c.c. Between 700 and 800 units of insulin were injected subcutaneously, the intravenous route being impossible on account of fibrosis and collapse of the veins. She died two hours after admission without regaining consciousness, the blood-sugar at death being 1,500 mg. per 100 c.c. She had herself taken a considerable amount of insulin before she went into coma, and she must have had well over 1,000 units in the twenty-four hours immediately preceding death. Another striking feature of the case was a raised basal metabolic rate, despite a slightly hypothyroidic appearance. On 12.1.34 the basal metabolism was 47 per cent. above normal and on 9.8.34 was 49 per cent. above normal. By 3.6.36 it had fallen to 16 per cent. above normal, despite a loss of weight. The thyroid gland was not enlarged. The Wassermann reaction was negative.

*Post-mortem examination.* An autopsy was performed by Dr. John Anderson. The findings were as follows: Heart slightly enlarged. There was oedema and congestion of the right lung and a similar, but less marked, condition of the left lung. The abdominal wall, mesentery, and omentum showed increase of fat. The stomach was normal. There were some duodenal diverticuli. The liver was normal in size, pale, with evidence of fatty degeneration; it contained glycogen. The gall-bladder contained a small cholesterol stone. The pancreas was adherent to the stomach and showed some fatty infiltration, but was otherwise normal. The uterus and right ovary had been removed, the left ovary was fibrotic. The brain was oedematous; there was atrophy of the right pre-central convolution.

*Histological examination:* There was extensive fatty degeneration of the liver. The pancreas had undergone autolytic changes and sections were unsatisfactory. The suprarenals showed post-mortem changes and loss of staining properties, the cells being somewhat dissociated. The pituitary gland was normal in size, hyperaemic, and the cells dissociated. The proportion of basophil and eosinophil cells was normal. Sections of brain showed no distinctive features.

#### *Experimental Observations*

The experimental work on this patient was inevitably incomplete, owing to her death. Several of the investigations require confirmation, but as such an extreme tolerance to insulin is very rare, they are of interest even if, in some instances, they are inconclusive.

*Glucose tolerance.* The progressive nature of the condition from its first onset is shown in Fig. 1 by comparison of the blood-sugar curves following administration of 50 gm. of glucose by mouth. In February 1930 the curve was that of a moderate case of diabetes, the fasting level being only slightly raised. By August of the same year the fasting level was 312 mg. per 100 c.c. and the rise in blood-sugar was much greater, though it should be noted that the turn in the curve on this date commenced earlier. By February 1936 the tolerance for glucose appeared to be slightly greater, yet, as shown below, *in February 1936 insulin failed entirely to diminish the hyperglycaemia following glucose.* The improvement in sugar tolerance on this date, compared with that of August 1930, was therefore probably not due to a corresponding increase in the production of insulin by the patient herself; the change must have been due to alteration in one of the other factors concerned in glycogenic-glycogenolytic equilibrium. This is one reason for believing that the patient's condition was not due to diminution in the secretion of the islets of Langerhans. It has been shown that the insulin (Wilder, Smith, and Sandiford 1932; Blotner, 1934; Clark, Gibson, and Paul, 1935; Glen, 1934) and the carbohydrate content of the diet (Hamman and Hirschman, 1919; Sweeney, 1927; Himsworth, 1934, 1935), given for a period before doing such tests as the above, influence the response of the individual to carbohydrate. Staub (1922) and Traugott (1922) observed that if two equal doses of carbohydrate were given within a short time, the rise in blood-sugar following the first was much greater than the

rise following the second. This has come to be known as the 'Staub-Traugott' effect. Before each of the above tests the carbohydrate content of the patient's diet was the same, though the amount of insulin she had been receiving in February and August 1930 was much less than in February 1936.

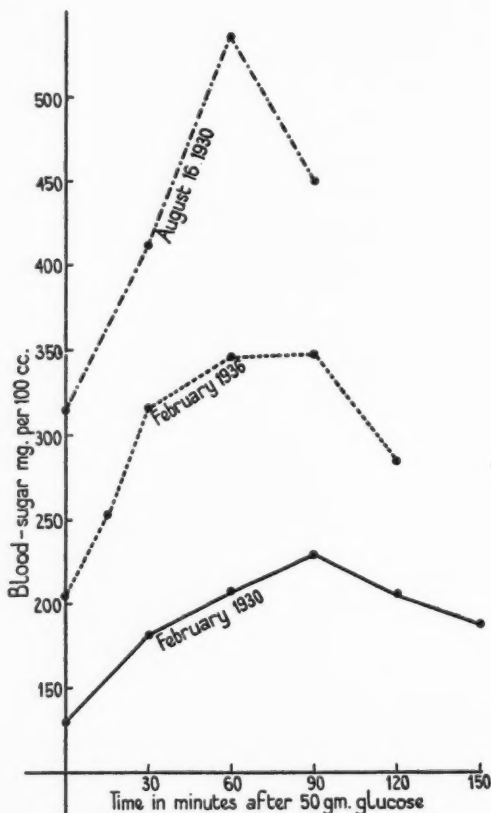


FIG. 1

*Effect of insulin on the sugar tolerance.* To determine whether insulin had any effect on the sugar tolerance, the patient was given a fixed diet and insulin dosage for some days. She then fasted for twelve hours, 50 gm. of glucose were given by mouth and the blood-sugar curve was followed. This was repeated a few days later, but 30 minutes before giving the glucose, 100 units of insulin were injected subcutaneously. A comparison of the blood-sugar curves (Fig. 2) shows that when insulin was given, the blood-sugar rose more rapidly and to a higher level than after glucose alone, though the fall in blood-sugar commenced earlier. The tolerance for glucose was therefore slightly *diminished* by giving insulin. These differences indicate that following the ingestion of carbohydrate, insulin at first delayed the removal of glucose

from the blood and later accelerated it. It must, however, be borne in mind that glucose was being excreted continuously from the kidneys during these experiments and that, in the curve after glucose and insulin, the glycosuria was greater than after glucose alone. A similar result was obtained by Falta (1924) in a patient whose blood-sugar rose slightly following administration of

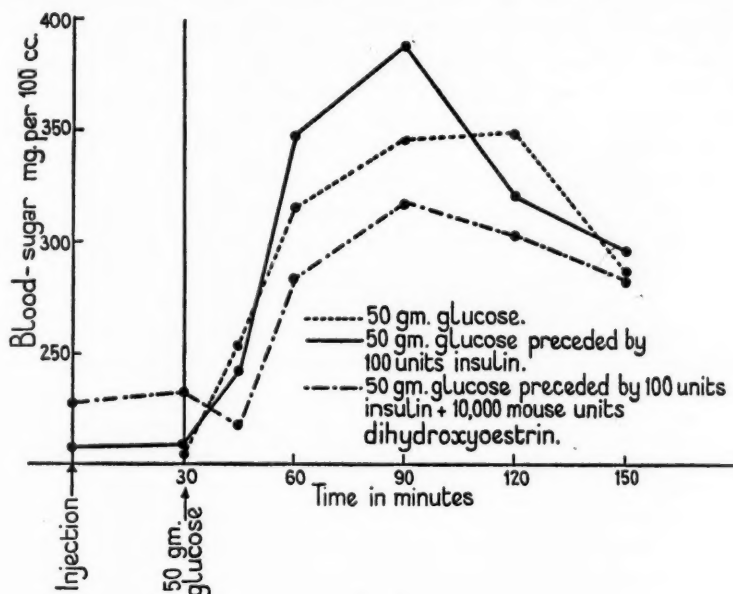


FIG. 2

insulin without glucose. He attributed this effect to the insulin having stimulated a mechanism which increased the blood-sugar to such an extent as to swamp the glycogenic action of the insulin.

*Influence of dihydroxyoestrin on the sugar tolerance.* It is now well established that the secretions of the anterior lobe of the pituitary gland and the gonads are antagonistic. Moore and Price (1932) state that 'The gonad principles of either sex exert a depressing effect on the pituitary which results in a diminished amount of sex-stimulating principle being available for the organism'. Barnes, Regan, and Nelson (1933) found that Amniotin (keto-hydroxyoestrin) diminished glycosuria in depancreatized dogs. Castration of animals results in hypertrophy of the pituitary (Rössle, 1914). Desclin (1935) found that Dimenformon (dihydroxyoestrin) caused increase of basophil and decrease of eosinophil cells in the pituitary of rats. Since our experiments, Tuchmann (1937) has shown that injection of keto-hydroxyoestrin diminishes the hypertrophied pituitary glands of castrated animals. Since it seemed probable that excess of pituitary secretion might be responsible for this patient's unusual reaction to insulin, and since ovarian secretion might be expected, on the above grounds, to have a synergic action with insulin, the patient was

given injections of one of these preparations. It has been shown (remarks by Dodds on Kaufmann, 1934) that dihydroxyoestrin is four times more effective in its action than ketohydroxyoestrin, and the former was, therefore, used. The patient was given 10,000 mouse units of dihydroxyoestrin (Progynon B Oleosum of Messrs. Schering) and 100 units of insulin subcutaneously, followed 30 minutes later by 50 gm. of glucose by the mouth, the carbohydrate ration and insulin treatment in the preceding days having been the same as before the other glucose tolerance tests described above. The resulting changes in the blood-sugar are shown in Fig. 2. The curves show that injection of dihydroxyoestrin and insulin had diminished the hyperglycaemia compared with that resulting from 50 gm. of glucose alone, or glucose preceded by insulin. The dihydroxyoestrin injections relieved the patient's pruritus and she was therefore given injections of 10,000 mouse units daily for eight days with much benefit. Others have reported similar results with female sex hormones. Carnot, Terris, and Caroli (1928) described a case relatively unresponsive to insulin, but which responded well when injections of ovarian extract were given. Rathery and Rudolf (1928) found that insulin was more potent in lowering the blood-sugar in female patients when menstruating, and that this corresponds with the maximum concentration of ovarian hormones in the blood. They used, however, very small doses of ovarian extracts in their experimental work. Cannavò (1936) found benefit to result to a patient whose insulin response was poor when folliculin (ketohydroxyoestrin) was given. Nelson and Overholser (1936) found that ketohydroxyoestrin reduced hyperglycaemia following injection of pituitary extracts in monkeys, attributing the effect to the influence on the pituitary gland. The work of Rathery, Kourilsky, and Gibert (1928*a*, 1928*b*) has shown that ovarian extracts (Hormovarine) influence the response of the dog to a given dose of glucose and that ovariectomy modifies the animal's response. Rathery, Kourilsky, and Laurent (1928) have shown in pancreatectomized animals that the effect of ovarian extract on the sugar tolerance is inverted. These results indicate the importance of the sex hormones in carbohydrate metabolism, and suggest that ovariectomy of our patient may have been an important factor in her disease. On the other hand, Collens, Slo-Bodkin, Rosenbliett, and Boas (1936) and Jones and MacGregor (1936) were unable to find any influence of oestrogenic hormones on the carbohydrate metabolism of human subjects.

*Effect of exercise on the blood-sugar.* The patient was given neither breakfast nor insulin, the blood-sugar was estimated and she then took exercise by walking up and down stairs in the hospital. The blood-sugar was estimated at intervals for almost two hours by which time she was feeling fatigued. As shown in Fig. 3, the blood-sugar rose slightly, but continuously, during this period. Moderate exercise has been shown to cause a slight increase in the blood-sugar (Rakestraw, 1923; Dill, Edwards, and Mead, 1935; Schlutz, Hastings, and Morse, 1935). At the stage of exhaustion in man (Levine, Gordon, and Derick, 1924) and in the dog (Schlutz, Hastings, and Morse, 1935) a marked fall in the blood-sugar was found. This is contrary to the findings

of Dill, Edwards, and Mead (1935) in the human subject, where exhaustion was found to be associated with a marked rise. Since our experiments Smith and Smith (1937) have shown that in normal subjects and in controlled diabetics, exercise diminishes hyperglycaemia following ingestion of food, but fails to do so in uncontrolled diabetics. While the exercise which our patient

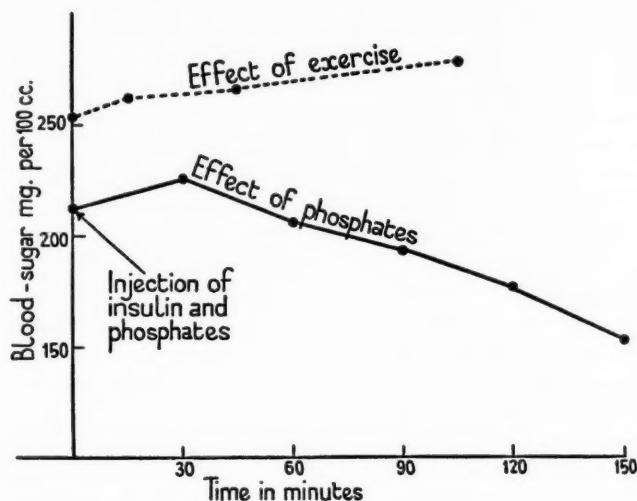


FIG. 3

performed was arduous, she did not become exhausted; and it is possible that had she continued, there would have been a fall in the blood-sugar. Her response to exercise would thus seem to have been normal.

*Effect of phosphate administration on the blood-sugar.* During the removal of glucose from blood under the action of insulin there is a diminution in the plasma phosphate (Wigglesworth, Woodrow, Smith, and Winter, 1923; Cori and Cori, 1933). The possibility of lack of available phosphate being the cause of the patient's condition was considered, and she was therefore given large doses of phosphate intravenously and by mouth. Owing to her death, however, it was not possible to investigate fully the changes in her blood phosphorus after giving carbohydrate and insulin. No food was given to the patient for twelve hours. At the end of this period the fasting blood-sugar was 212 mg. per 100 c.c. She was then given 400 units of insulin subcutaneously and 20 c.c. of a phosphate solution intravenously (16.1 c.c. of 0.947 per cent.  $\text{Na}_2\text{HPO}_4$  and 3.9 c.c. of 0.908 per cent.  $\text{KH}_2\text{PO}_4$ , this solution having a pH of 7.4). No glucose or food was given and the blood-sugar was estimated every half hour. The course of the blood-sugar is shown in Fig. 3. After the conclusion of this experiment the patient was given her diet and insulin (100 gm. carbohydrate, 75 gm. protein, 150 gm. fat with 1,050 units insulin) exactly as previously, but the hyperglycaemia and glycosuria diminished progressively until two days later there was only a trace of sugar

in the 24 hours specimen of urine, and the blood-sugar 4 hours after a meal containing 30 gm. carbohydrate was 117 mg. per 100 c.c., the lowest blood-sugar ever found in this patient. In view of these results large doses of phosphates were given by mouth for a week, but despite these, the hyperglycaemia and glycosuria gradually returned to their original levels.

*Effect of frequent administration of insulin.* It is recognized that several small doses of insulin are usually more effective in keeping the blood-sugar in diabetes low than one large dose. The patient was therefore given the same total dose of insulin in the day (1,050 units) divided into eight injections at intervals of two hours during the day, but the results were no better than when three large doses were given. Glassberg, Somogyi, and Taussig (1927) likewise found fractional doses of no benefit in their case.

*Effect of withholding all insulin.* Since insulin appeared rather to increase, than to decrease the blood-sugar, on two occasions during the patient's stay in hospital insulin was withheld. On both occasions ketones very rapidly appeared in the urine in abundance and insulin administration had to be recommenced to prevent coma. This effect of insulin, even when it seemed to be ineffective in reducing the blood-sugar, has been noted on more than one occasion (Lawrence, 1927, 1928; Altshuler, 1935; Widai, Abrami, Weill and Laudat, 1935).

*Effect of patient's serum on response of rabbits to insulin.* It was considered possible that the patient's serum might contain some substance which prevented the normal action of insulin and that by injecting it into rabbits a corresponding diminution in the action of insulin in them might occur. There was also the possibility that it was the introduction of insulin into the blood and tissues which stimulated the production in the patient of an 'insulin antagonistic' factor, and accordingly two series of experiments were performed (a) with serum drawn from the patient many hours after she had received insulin, and (b) with serum drawn a few minutes after a massive dose of insulin. A dose of 0.2 units of insulin was mixed with four volumes of sterile saline, to make it more accurately measurable, and injected into the marginal vein of the ear of a fasting adult rabbit, the animal's blood-sugar being determined for two hours thereafter. Not less than two days later 2 c.c. of the patient's serum was mixed with 0.2 units of insulin in saline and the mixture injected into the fasting rabbit, the blood-sugar being determined as before. Not less than forty-eight hours after the injection of serum, insulin and saline alone were again injected and the blood-sugar curve followed. The sera were taken from the patient (a) sixteen hours after having had food or insulin, and (b) thirty minutes after receiving 400 units of insulin subcutaneously, but sixteen hours after food. Controls were performed by injecting sera from healthy subjects, sera from diabetics normally responsive to insulin, and serum from the patient (before and after giving her 400 units of insulin) without admixture with insulin. As it was not possible to inject the sera into the animals immediately after withdrawal from the patient, the sera were stored in a frozen condition. The

results appear in Figs. 4 to 8. Fig. 4 shows the effect on a rabbit's response to insulin of injecting simultaneously with the insulin, 2 c.c. of the patient's serum, the serum being drawn sixteen hours after she had had insulin. It is seen that the serum diminished the degree of hypoglycaemia produced by the insulin. Furthermore, forty-eight hours after injection of the serum,

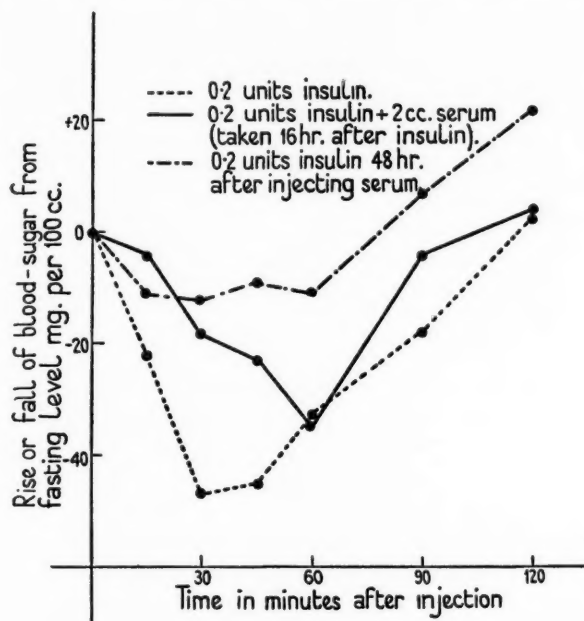


FIG. 4

the animal's response to insulin had not returned to normal, but was still further diminished. Fig. 5 illustrates the results when serum injected into the rabbit was taken thirty minutes after the patient had had 400 units of insulin. The effect of the serum in this instance is more marked than when the serum was drawn some considerable time after the patient had had insulin. Forty-eight hours later insulin and saline, without serum, were again given. After an initial fall the blood-sugar rose to a very high level forty-five minutes after insulin, falling in 120 minutes to a level considerably below the fasting. In Fig. 6 is seen the corresponding experiment with serum taken *post mortem*. Here also, injection of serum along with insulin markedly diminished the hypoglycaemia produced by insulin. It must be remembered that this post-mortem serum corresponds to that taken after giving the patient a large dose of insulin, for she had received very large amounts just before death. Control experiments using serum from a normal subject are shown in Fig. 7. There was very slight diminution in the hypoglycaemia produced by insulin when normal serum was simultaneously injected, but of much less degree than that with the patient's serum and, in

the case of the normal serum, the effect forty-eight hours later was diminished and not increased. Injection of the patient's serum without insulin, whether

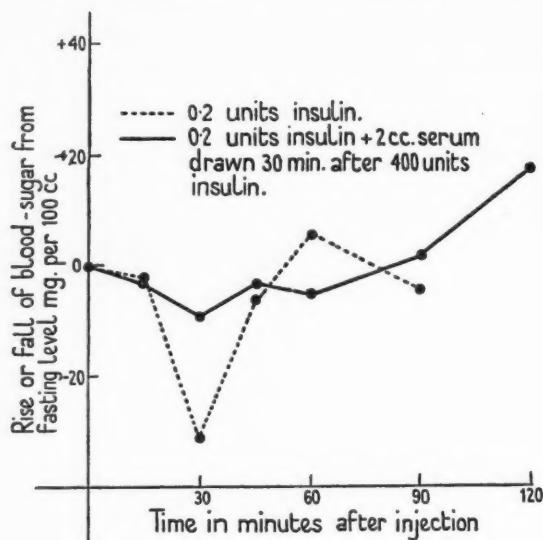


FIG. 5

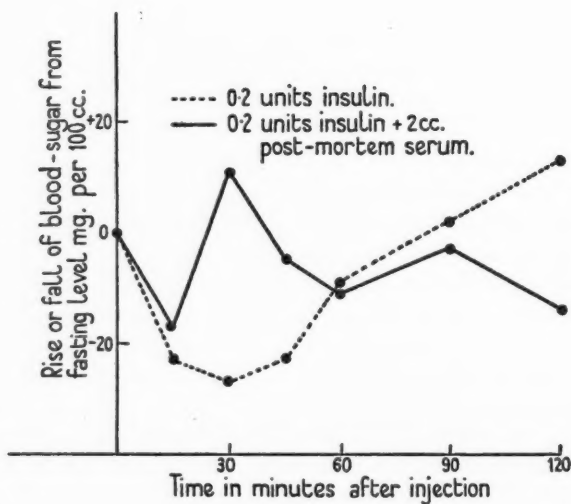


FIG. 6

taken some time after giving her insulin or just after an injection of 400 units, did not appreciably affect the animal's blood-sugar (Fig. 8). Control experiments using serum from diabetic subjects normally responsive to insulin gave

variable results, the significance of which is uncertain. It is hoped to investigate this matter further. It seems possible that the sera of certain

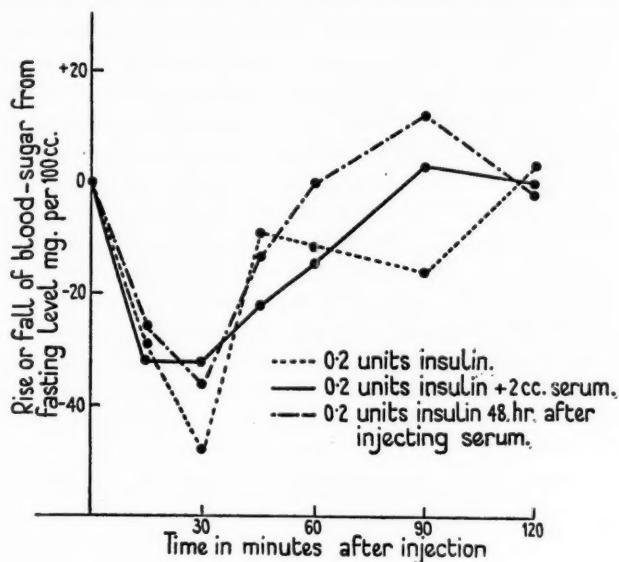


FIG. 7

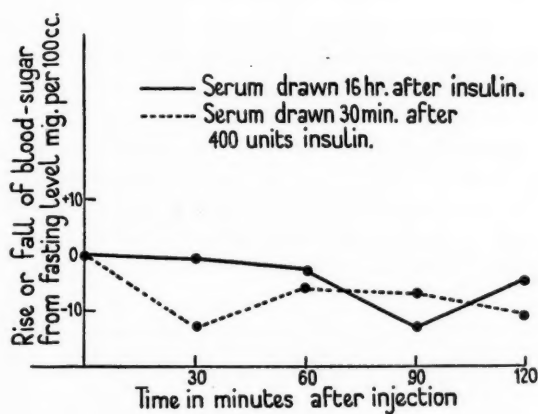


FIG. 8

types of diabetic patients have the property of conferring some degree of insulin antagonism on animals. This view is supported by the work of de Wesselow and Griffiths (1936).

*Discussion*

The term 'insulin resistance' has been indiscriminately applied to cases requiring very large doses of insulin daily, such as the case we have just described, and to those which require moderate daily doses. MacBryde (1933) and others have shown that many cases requiring very little insulin might be classed as 'insulin resistant' on account of their response to insulin being much less than usual; in fact, it seems probable that there are persons who do not normally have any hyperglycaemia, yet have a degree of 'resistance' to insulin. We prefer, therefore, to use the term 'insulin antagonistic' suggested by Aubertin (1936), with reference to our case, since the condition was not merely one of diminished response to insulin, but an active antagonism to it when administered. Cases tolerating very large doses of insulin (500 units or more daily) have been associated with a great variety of conditions, e.g. hyperthyroidism (Hills, Sharpe, and Gay, 1934); haemochromatosis (Allan and Constam, 1928; Root, 1929; Engel, 1934); allergy (Taussig, 1927; Allan and Scherer, 1933; Karr, Scull, and Petty, 1933; Rudy, 1931); acidosis (Labbé and Boulin, 1934); cardiac disease (Clay and Lawrence, 1935); damage to the mid-brain (Mason, 1931); pituitary disorders other than acromegaly (Cannavò, 1936); hepatic disorders (Root, 1935), following X-ray therapy of a tumour (Cannavò, 1936). In less marked cases, acromegaly (Wemyss, 1927; Ulrich, 1928), tuberculosis (Wayburn, 1935) and wide-spread splanchnic thrombosis (Pollak and Long, 1932) have also been implicated. In diabetic coma, of course, very large doses are tolerated, e.g. Thannhauser and Fuld, (1933); Byworth, (1928), and Jamieson (1934). We have ourselves given 700 units within twenty-four hours to comatose patients. Zeckwer (1931) records the occurrence of spontaneous 'resistance' of high degree in two rabbits which he attributed to the influence of the sympathetic nervous system. From the amount of insulin required to keep a depancreatized dog, fed on ordinary diet, with its blood-sugar at a normal level, Root (1929) calculated that a man of average weight would require to produce 200 to 300 units of insulin daily. Consequently in any patient requiring substantially more insulin than this there is probably some other factor than lack of insulin responsible for the condition. Lack of response to insulin may arise in at least four different ways:

1. From lack of absorption of insulin. When the hormone is given subcutaneously, this may be due to induration of the tissues, sclerosis of the vessels, or defective circulation.

2. Absence of some other essential factor. Insulin is undoubtedly only one factor in the production of glycogenesis and though it is present in abundance one of the other factors may be missing. This view has been put forward by Taussig (1927), and Glassberg, Somogyi, and Taussig (1927) have suggested that this additional factor is a 'co-enzyme'. It has been variously termed 'Glykomutin', 'Phosphatase', and 'Insulin complement',

and is said to be necessary if insulin is to convert glucose to glycogen. The part played by phosphates in carbohydrate metabolism is not yet clear, but they are certainly concerned in the reactions which follow secretion of insulin (Markowitz, 1926) and it is likely that they are one of the essential requirements in removal of glucose from the blood. Himsworth (1932, 1933, 1934) believes that insulin, as secreted by the pancreas, is inactive and must be activated by a 'kinase'. Failure of such a kinase could, of course, be a cause of insulin insensitivity, but Himsworth does not imply that injected insulin is inactive.

3. Neutralization of insulin either by destruction or chemically or physiologically. That is to say, the 'insulin resistant' person produces some substance in the body which either destroys the insulin, combines with it to make it inactive, or else a substance which antagonizes the action of insulin. Rosenthal and Behrendt (1926) and Depisch and Hasenöhrl (1928) have shown that pus will destroy the properties of insulin *in vitro*, and it seems possible that the increased insulin tolerance of patients with sepsis may be due to destruction of insulin in the body. With regard to antagonism to insulin, it is, of course, certain that adrenaline and thyroxine have this action, and more recently it has been shown that one or more of the pituitary hormones share this property. MacCallum (1935) claims to have found an insulin antagonistic substance in duodenal extracts, but its mode of action is unknown. The insulin antagonism which has given rise to most investigations in recent years, however, is that believed to be associated with the pituitary gland, and this is discussed more fully below.

4. Loss of tissue in which glycogen can be stored (Boller and Überrack, 1932; Labbé, 1924; Carrière, Gineste and Belbenoit, 1935). Probably this is the explanation of the lack of response to insulin in haemochromatosis, since so much of the liver parenchyma is lost.

In considering the experimental evidence from our patient, the following facts have to be considered:

1. Enormous doses of insulin failed to lower the blood-sugar.
2. Insulin tended to decrease the sugar tolerance.
3. Dihydroxyoestrin increased the sugar tolerance.
4. Insulin and intravenous administration of phosphate lowered the blood-sugar.
5. The patient's response to exercise was normal.
6. The basal metabolism was considerably increased.
7. Injection of the patient's serum into rabbits diminished their response to insulin and induced a degree of insulin antagonism in them.
8. If insulin were not administered, acidosis rapidly supervened.
9. There was a family history of diabetes.
10. The diabetic symptoms commenced after ovariectomy and subtotal hysterectomy.

The history of the case and the experimental findings exclude non-absorption of insulin as a cause of the patient's condition, and the post-

mortem findings exclude loss of glycogen storing tissue. Since the patient's tolerance for sugar was slightly greater in August 1936 than in August 1930, despite the fact that in 1936 insulin failed to lower the blood-sugar, and since injection of insulin actually decreased the sugar tolerance, the patient's condition cannot have been due solely to failure of insulin to act, or to its destruction. The rapid appearance of ketosis when insulin administration was stopped is further evidence against the suggestion that the insulin was destroyed, since it shows that the insulin had some influence on the patient's metabolism. De Wesselow and Griffiths (1936) have shown that the sera of certain diabetic patients will diminish the response of rabbits to insulin, and they believe that this is due to the sera containing some substance which will modify the hypoglycaemic action of insulin. With serum from our patient we found that forty-eight hours after injecting the serum into a rabbit, the animal's response to insulin had still further decreased compared with the response when serum and insulin were simultaneously injected. Since we injected the serum intravenously, the change in response forty-eight hours later is unlikely to have been due to gradual absorption, and we suggest that the serum contained a substance which stimulated the rabbit itself to produce something antagonistic to glycogenesis or which increased glycogenolysis or neoglucogenesis. Injection of the patient's serum alone failed to alter the animal's blood-sugar significantly; the serum apparently could only modify the response of the animal to injected insulin. The actual mechanism whereby this occurs is difficult to understand, for presumably the animal was producing endogenous insulin which did not appear to produce any unusual response. The interpretation of these results must await further investigation.

The effects of giving phosphates and dihydroxyoestrin also support the view that insulin deficiency was not the cause of the patient's condition, but it is difficult to explain the findings in view of the results of the animal experiments. These experiments imply that the defect was not merely absence of something necessary for insulin to act, yet phosphates markedly lowered the blood-sugar for a period, and since these were effective only when given parenterally it is suggestive of failure to absorb phosphates from the alimentary tract. Had a full investigation of the patient's phosphorus metabolism been possible, the explanation might have been apparent.

With regard to dihydroxyoestrin, this hormone, as has been mentioned, antagonizes anterior pituitary secretion. The factor which antagonizes insulin probably arises in the anterior lobe of the pituitary gland and the effect of dihydroxyoestrin was probably to counteract the production of the insulin-antagonistic substance. The absence of the uterus and an ovary from the patient would diminish her endogenous supply of oestrin and this may well have been a contributory factor in her condition.

The evidence for the presence in the anterior lobe of the pituitary gland of a hormone which influences carbohydrate metabolism is now so broadly based as to be practically conclusive. The classical work of Houssay and his

collaborators on the effects of hypophysectomy in toads and dogs has clearly shown the antagonism between the anterior lobe of the pituitary gland and the internal secretion of the pancreas (Houssay and Biasotti, 1930*a*, 1930*b*, 1930*c*, 1931, 1933). They have also shown that injections of extracts of the anterior pituitary, or implantation of the gland, will nullify the effects of hypophysectomy, or, in a normal animal, cause hyperglycaemia and glycosuria (Houssay, Biasotti, Benedetto and Rietti, 1933*a*, 1933*b*; Houssay, Benedetto and Mazzocco, 1933; Houssay, 1933; Houssay and Foglia, 1936). The quantitative effects of such injections are to some extent governed by the previous diet (Houssay, Biasotti and Rietti, 1934). For an excellent summary of this work, with bibliography, see Houssay (1936). This work was in part anticipated by Johns, O'Mulvenny, Potts and Laughton (1927) and has been confirmed by the work of Baumann and Marine (1931), Regan and Barnes (1933), Mahoney (1934), Soskin, Mirsky, Zimmermann and Crohn (1935), Karlik (1936), Slome (1936), Pencharz, Cori and Russell (1936), and Young (1937). An abnormal sensitivity to insulin in dogs was observed by Geiling, Campbell and Ishikawa (1927) after clamping the stalk of the pituitary gland, but they failed to find this effect after hypophysectomy. The anterior lobe of the pituitary causes (probably) increase of hepatic glycolysis (Campos, Curutchet and Lanari, 1933; Johns, O'Mulvenny, Potts and Laughton, 1927).

Anselmino and Hoffmann have shown that after ingestion of carbohydrate by a normal person a 'carbohydrate metabolism hormone' can be found in the blood which, when injected into rats, reduces the glycogen content of the liver. This substance is found in excess in the blood of diabetics, even when fasting. It is also found in animals, but hypophysectomy results in its disappearance. An extract with a similar action can be obtained from the anterior lobe of the pituitary gland (Anselmino and Hoffmann, 1934). They claim also to have obtained this substance from the urine of diabetics (Anselmino and Hoffmann, 1935, 1936*a*). Pancreatectomy does not result in an increase of the hormones in the blood (Anselmino and Hoffmann, 1936*b*), but injection of insulin prevents its appearance. These authors (1931*a*, 1931*b*) claim also to have found a corresponding hormone produced after ingestion of fats. Boenheim and Heimann (1932) have found an extract of the anterior pituitary which will increase the ketones in the blood, and Burn and Ling (1933) have shown that it will increase the ketones in urine. (See also Steppuhn, 1934.) Anselmino and Hoffmann (1933*a*, 1933*b*) and Anselmino, Herold and Hoffmann (1933) claim also to have found a pituitary hormone causing hypertrophy of the islets of Langerhans, thus resulting in inhibition of the so-called 'carbohydrate metabolism hormone' by increasing production of insulin. Their investigations in relation to these hormones indicate the importance of a well-balanced fat-carbohydrate diet (Anselmino and Rhoden, 1936). Further evidence in support of the presence of a diabetogenic substance in the blood is given by the experiments of Képinov and Dutailis (1928, 1931) who showed that transfusion of diabetic blood into animals resulted in

hyperglycaemia. Képinov and Guillaumie (1934) showed that the pituitary has an influence on the production of insulin. Venkatachalam and Ratnagiriswaran (1935) have shown that extract of the anterior pituitary will increase the blood-sugar level. A contribution of great significance to the understanding of the action of the pituitary gland on carbohydrate metabolism was made by Soskin, Mirsky, Zimmermann and Crohn (1935) who showed that the hypophysectomized dog is unable to produce carbohydrate from stored or exogenous fat, that is, there can be no gluconeogenesis from fat, but only from protein. They point out the absence of ketonuria in the depancreatized-hypophysectomized dog, even when the blood-sugar is high. We have already referred to the remarkable absence of ketonuria in our patient until the last stages of her illness and we consider this as additional evidence for the pituitary origin of her disease. Further evidence in support of the pituitary origin of these hyperglycaemias is the fact that cases of acromegaly and Cushing's pituitary basophilism, in which there are demonstrable tumours of the anterior lobe of the pituitary, are usually associated with glycosuria and hyperglycaemia relatively non-responsive to insulin. Fry (1915) and Glen (1934) have observed histological changes in the anterior lobe of the pituitary in certain cases of diabetes—usually acute diabetes in young persons.

Various workers have attempted to improve cases whose response to insulin was poor by irradiation of the pituitary gland. In most instances an improvement is recorded (Cannavò, 1936; Pière and Sarradon, 1935; Merle, 1935). Barnes, Culpepper and Hutton (1935) irradiated both the pituitary and adrenal regions with beneficial results. Selle, Westra and Johnson (1935) failed to find any benefit by irradiating the pituitary gland in depancreatized dogs. Pijoan and Zollinger (1937) could find no alteration in the carbohydrate metabolism after irradiating the pituitary gland. The obvious difficulty in attempting therapy by this method is, of course, the impossibility of affecting only one part of the gland.

Several investigators have attempted to demonstrate the presence of an insulin-antagonistic factor in the blood by injecting animals with serum. Karelitz, Cohen and Leader (1928) claim that normal human plasma and, in greater degree, diabetic plasma, will destroy the action of insulin on the blood-sugar when the plasma and insulin are incubated together. Glassberg, Somogyi and Taussig (1927) injected 10 c.c. of serum from a patient who could tolerate very large doses of insulin, into rabbits, but could detect no alteration in the rabbits' response to insulin. Depisch and Hasenöhl (1928) found that serum from a diabetic with septic complications, when mixed with insulin and injected into a rabbit, prevented the normal action of insulin. Similar experiments with serum from a diabetic with tuberculosis and a third patient without infective complications failed to affect the action of insulin on animals. De Wesselow and Griffith's work, already referred to, has shown that the plasma of normal persons and young diabetics does not alter the response of animals to insulin, but that plasma from elderly diabetics diminishes

the response. These various experiments go to show that, apart from sepsis, there is something in the plasma of certain cases which prevents insulin acting normally. De Wesselow and Griffiths believe that the inhibition of insulin action in their cases was due to antagonism of pituitary origin.

In reviewing the cases recorded in the literature which were able to tolerate large doses of insulin, the condition of several appears to be associated with some kind of sensitization. Falta's (1924) case has already been mentioned. In a case described by Lawrence (1928) there was a marked eosinophilia. In the case described by Karr, Scull and Petty (1933) the insulin refractory condition disappeared after an injection of serum taken from a rabbit which had previously had an injection of the patient's serum plus insulin, and was therefore presumably sensitized to the patient's serum. This suggests that their patient had some type of sensitization.

Häusler and his co-workers have examined the problem of diminished response to insulin in a somewhat different manner. They have studied the rate at which erythrocytes will remove glucose from plasma under different conditions. The rate of removal of glucose from plasma is normally greater after ingestion of glucose, the pancreas being essential for this effect (Häusler and Loewi, 1927*b*) and the rate of removal of glucose is accelerated by adding insulin. Diabetic plasma loses glucose to the cells less rapidly than normal plasma (Häusler and Loewi, 1927*a*), though plasma from insulin resistant cases loses glucose as rapidly as normal plasma. Insulin, however, fails to accelerate the disappearance of glucose from the plasma of resistant cases (Häusler and Höglér, 1927). These authors believe that there is a specific substance which prevents the absorption of glucose by cells and have named it 'Glykämín', (Dietrich, Häusler and Loewi, 1927.) This substance, together with insulin, forms a balanced system, the one assisting, the other inhibiting absorption of glucose. It is suggested that this substance is responsible for diabetes (Dietrich and Loewi, 1927). Mauriac and Aubertin (1928*a*, 1928*b*, 1928*c*) showed that normal and diabetic blood would inactivate insulin, but that diabetic blood was more potent in doing so. They believe that the differences are due to differences in the permeabilities of the red blood-cells. Similar results were obtained by Karelitz, Cohen and Leader (1930*a*, 1930*b*).

There is no one cause for insulin antagonism in our patient to which we can point with certainty, but there is considerable evidence to show that she had an active antagonism, not merely a diminished response to insulin, and this view is supported by some previously recorded experiences. There is evidence to show that she had a specific insulin-antagonistic substance in her blood, and recent work suggests that the anterior lobe of the pituitary gland was the probable source of this.

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*Summary*

1. A case of diabetes is described in a woman with a family history of diabetes, the diabetes commencing after removal of the uterus and an ovary. The patient received 1,050 units of insulin daily for a considerable period.
2. When insulin was given with glucose, the glucose tolerance was less than when no insulin was given.
3. When insulin administration was stopped ketosis rapidly developed.
4. Injection of dihydroxyoestrin increased the glucose tolerance.
5. The changes in the patient's blood-sugar during exercise were normal.
6. Parenteral administration of phosphates lowered the blood-sugar.
7. Phosphates given by mouth did not affect the blood-sugar.
8. Fractional doses of insulin were no more effective than few and large doses.
9. Injection of the patient's serum into rabbits induced an active insulin antagonism in the rabbits. The antagonism was more marked if the patient had had insulin before withdrawing the serum.

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EXOPHTHALMIC OPHTHALMOPLÉGIA<sup>1</sup>

By W. RUSSELL BRAIN

(With a Pathological Report on the Ocular Muscles and Thyroid Glands  
by HUBERT M. TURNBULL)

With Plates 21 to 23

*Introduction*

THE multiplication of syndromes is not to be undertaken without sound justification. Nevertheless, the progress of clinical medicine has consisted to an important extent in the recognition of differences in clinical material previously thought to be homogeneous as, for example, in the recent differentiation of the anaemias. The association of ophthalmoplegia with exophthalmos and general symptoms of thyrotoxicosis has been known for over eighty years. Hitherto the ophthalmoplegia has been regarded either as an unusual complication of exophthalmic goitre, or as evidence of the association of myasthenia gravis with this disease. Certain clinical features, however, observed in the study of 31 cases extending over seven years, and taken in conjunction with the recent increase in our knowledge of the physiology of the thyroid gland, have convinced me that neither of these views is correct and that 'exophthalmic ophthalmoplegia' is a syndrome distinct from both exophthalmic goitre and myasthenia gravis. Briefly, these distinguishing features are that exophthalmic ophthalmoplegia differs from exophthalmic goitre in both age and sex incidence, and, a point of cardinal importance, in the rôle of the thyroid in its aetiology. Whereas in Graves' disease thyrotoxicosis is an essential, and indeed the principal, disorder of function, in exophthalmic ophthalmoplegia thyrotoxicosis plays no essential part. Omitting exophthalmos, which as will be seen later cannot now be regarded as primarily a symptom of thyrotoxicosis, thyrotoxic symptoms though usually present are generally slight; and in an important group of patients in whom exophthalmic ophthalmoplegia develops after thyroidectomy may be altogether absent, the basal metabolic rate being normal or even subnormal. Corresponding to this we find that thyroidectomy, in marked contrast to its beneficial influence in Graves' disease, may have little or no effect upon the main symptoms of exophthalmic ophthalmoplegia. In distinction from myasthenia gravis the paralysis in exophthalmic ophthalmoplegia is limited, save in very rare cases, to the ocular muscles. These, moreover, do not exhibit the

<sup>1</sup> Received January 10, 1938.

characteristic fatiguability of myasthenia and do not show an improvement in power as a result of the administration of prostigmin. Furthermore, patients with exophthalmic ophthalmoplegia do not exhibit either the variability in their symptoms or the downhill course which are typical of myasthenia. Almost invariably, in fact, the disorder becomes arrested, though complete recovery from the ophthalmoplegia is unusual. The name 'exophthalmic ophthalmoplegia' which I have suggested for this syndrome, although cumbersome, describes the two cardinal symptoms and possesses the advantage of suggesting both an affinity with and a difference from exophthalmic goitre. Unfortunately it is not exclusively descriptive since both exophthalmos and ophthalmoplegia may occur in other conditions. 'Thyrotoxic ophthalmoplegia' would be a misnomer since the syndrome may occur in the absence of thyrotoxicosis. The term 'malignant exophthalmos' which is sometimes used by American writers (Rosenbaum, 1937; Ruedemann, 1937) is not very appropriate, partly on account of the association of the term 'malignant' with new growth and partly because this epithet cannot suitably be applied to the milder cases. Naumann (1853) first described the association of ophthalmoplegia with thyrotoxicosis in a middle-aged man whose eyeballs were both prominent and also immovable. Warner (1883) reported in detail the case of a woman who was admitted to the London Hospital with well marked signs of Graves' disease, including bilateral exophthalmos, and marked limitation of the movements of both eyes in all directions. In addition there was weakness of the muscles of mastication, the facial muscles, and the limb muscles. Following treatment, which included 15 gr. of potassium iodide three times a day, the patient made an excellent recovery, except that proptosis and considerable ophthalmoplegia persisted. Warner's patient later passed under the care of Bristowe (1886). Fresh symptoms, attributed to hysteria, developed, and she died two years later of acute bronchitis. At autopsy no abnormality was found in the nervous system, but there was a good deal of fat in the orbits, the ocular muscles were unusually pale and seemed stretched, and the thyroid lobes were somewhat large. Ballet (1888) reported two further cases and the condition became known as 'Ballet's sign'. Ballet drew attention to the normal pupillary reactions in spite of the external ophthalmoplegia and to the escape in one case of the levator palpebrae superioris. Many subsequent writers have published isolated cases, only the more important of which need be quoted. The earlier authors concerned themselves mainly with clinical descriptions of the palsies. Sattler (1909, 1910) in his monumental treatise 'Die Basedow'sche Krankheit' reviewed the literature up to 1910, and Kappis (1911) reported two additional cases of ophthalmoplegia and two cases of bulbar palsy complicating Graves' disease, and discussed the previously published cases. Heuer (1916) reported a case in which both ophthalmoplegia and bulbar palsy were present and reviewed 80 cases of 'cerebral nerve palsies' in exophthalmic goitre to be found in the literature up to that time. Wedd and Permar (1928) reported a patient with partial

ptosis and almost complete external ophthalmoplegia, and later dysphagia, who came to autopsy. No mention is made of the ocular muscles, but serial sections of the brain showed no lesions. The thyroid showed changes somewhat atypical for exophthalmic goitre. Moore (1920) described oedema of the orbital fat and extra-ocular muscles in a patient with extreme exophthalmos. Burch (1929) reported two cases of ophthalmoplegia, with special reference to the changes found in one case in the extra-ocular muscles which were greatly enlarged and exhibited oedema, degeneration and atrophy with dense infiltration with lymphoid and plasma cells, and fibrosis. Zimmerman (1929) reported eight cases of progressive exophthalmos following thyroidectomy, and Thomas and Woods (1936) have recently reported 15 further cases in which progressive post-operative exophthalmos occurred with a normal or subnormal basal metabolic rate in all but one case. Ophthalmoplegia was present in seven cases. In three cases in which the extra-ocular muscles were examined the typical lymphocytic infiltration was observed. Naffziger (1931) has devised an operation of orbital decompression for the relief of the exophthalmos.

#### *Clinical Features*

This paper is based upon a study of 31 patients, 30 of whom have been under my own observation during the past seven years. The remaining patient is included because in this case there was post-mortem material available. In 29 of the 31 patients exophthalmic ophthalmoplegia arose spontaneously; in the remaining two it developed after the operation of subtotal thyroidectomy.

*Age and sex incidence.* There is a marked contrast between exophthalmic ophthalmoplegia and exophthalmic goitre in respect of age and sex incidence. Exophthalmic goitre is a disorder chiefly of early adult life, exophthalmic ophthalmoplegia of middle age. In Joll's (1932) series of female cases of primary hyperthyroidism only 30·6 per cent. were over 40, and in his combined series of female cases of primary and secondary hyperthyroidism 39 per cent. were over 40. In this series of patients with exophthalmic ophthalmoplegia, however, as the following table shows, 26 out of 31, or 84 per cent., were 40 or older.

Age.	Number.
0-19	0
20-29	1
30-39	4
40-49	11
50-59	9
60-69	6

The youngest was 23 and the oldest was 68. The average age was 49, compared with an average age of 36 in Joll's series. The proportion of males affected is much higher in exophthalmic ophthalmoplegia than in exophthalmic goitre. Joll quotes the Registrar-General's figures as showing

that the ratio of females to males affected with exophthalmic goitre is 9 to 1. In this series of cases of exophthalmic ophthalmoplegia 19 were females and 12 were males. In Thomas and Woods' (1936) series of 15 patients in whom progressive exophthalmos developed after thyroidectomy 11 were males and four were females.

*Mode of onset.* 1. Spontaneous cases. The onset of the disorder is usually subacute. As a rule the patient complains that one eye has become increasingly prominent during the previous three or four months and that double vision, due to ophthalmoplegia, has occurred during the same period. The other eye is usually later in developing exophthalmos or may never do so. Even if it does become prominent, it may not exhibit ophthalmoplegia. Another mode of onset is for both exophthalmos and ophthalmoplegia to develop simultaneously in both eyes in the course of three or four months. Less often, the onset is slower and more insidious and then double vision may be intermittent. Less often still, the onset is very acute, as in one patient, the only one whom I happened to see before the disorder developed, in whom exophthalmos and ophthalmoplegia appeared in both eyes in the course of a week. It is very rare for a patient to complain of any general symptoms of thyrotoxicosis before the ocular symptoms occur.

2. Post-operative cases. When the disorder follows subtotal thyroidectomy, there is usually a latent interval between the operation and the onset of exophthalmic ophthalmoplegia. Thomas and Woods (1936) state that in such cases the progressive exophthalmos may develop at any time between ten days and two years after the operation. In Zimmerman's (1929) series of eight cases the interval between the operation and the onset of symptoms ranged from three to twelve months. In the two post-operative cases of this series it was five months and sixteen months respectively. Thomas and Woods, and Zimmerman point out that there may have been no exophthalmos before operation. The development of the ocular symptoms in the post-operative cases is usually insidious and as a rule both eyes are affected.

*Exophthalmos.* Exophthalmos was present in all cases, being unilateral in six and bilateral in 25. In the unilateral cases the right eye was affected six times and the left eye not at all. In the bilateral cases the degree of exophthalmos was unequal in 16 and equal in eight, the right eye being the more prominent in six patients and the left in 10. In one patient, first one and then the other eye was the more prominent. An asymmetry in the protrusion of the eyes was thus present in 23 out of the 31 patients, the commonest finding being bilateral, but asymmetrical, exophthalmos. Readings were made with the Hertel exophthalmometer in 17 cases, usually on several occasions in each case. The average normal reading with this instrument is 12.5 mm. The following table contrasts the observations made on the 17 patients with exophthalmic ophthalmoplegia with those made on 20 consecutive cases of primary and secondary hyperthyroidism.

*Exophthalmometer Readings*

	Exophthalmic ophthalmoplegia. 17 cases.	Primary and secondary hyperthyroidism. 20 cases.
Average reading	19.4 mm.	15 mm.
Maximum readings in one patient	Right 20 mm. Left 27 mm.	Right 20 mm. Left 16 mm.
Average difference between eyes in asymmetrical cases	4 mm.	2 mm.
Maximum difference between eyes in asymmetrical cases		
(1) with unilateral exoph- thalmos	5 mm.	No cases
(2) with bilateral exoph- thalmos	8 mm.	4 mm.

These readings bear out the clinical observation that the exophthalmos is usually much greater in exophthalmic ophthalmoplegia than in exophthalmic goitre. Thus, if the normal reading be taken as 12.5 mm., the average amount of exophthalmos in cases of hyperthyroidism is 2.5 mm. while in exophthalmic ophthalmoplegia it is 7 mm. In the latter condition, also, an asymmetry in the degree of protrusion of the two eyes when present is commonly much greater than in exophthalmic goitre. Naffziger (1931) has reported a post-operative case in which the severity of the exophthalmos was considerably greater than in any case in this series, the exophthalmometer readings being, right 34 and left 32 mm., which is equivalent to a protrusion of 2 cm. The eye is always protruded straight forwards, though the occurrence of a squint as a result of ophthalmoplegia may make it appear that there is some other displacement of the globe, usually downwards. If one tries to press back the eye, one encounters a firm resistance which is especially evident in the unilateral cases on comparing the prominent with the normal eye. The exophthalmos is always associated with some oedema of the loose tissues of the upper and lower lids, and when there is much exophthalmos, the oedema may be considerable (Plate 21, Fig. 1). In such cases there is also oedema of the conjunctiva which gives it an abnormally glistening appearance and causes it to be thrown into folds at the canthi when the patient moves the eye to either side (Plate 22, Fig. 4). In severe cases corneal anaesthesia and ulceration may occur.

*Ophthalmoplegia.* The ophthalmoplegia was unilateral in 13 patients and bilateral in 18. Thus in seven patients the ophthalmoplegia was unilateral though the exophthalmos was bilateral. In such cases the ophthalmoplegia was always present on the side of the greater exophthalmos. The ophthalmoplegia is a paresis or paralysis, not of individual extra-ocular muscles, but of movement of the eye in a particular plane. This is evident in the case of the vertical movements where, except in mild cases, the superior rectus is never affected without the inferior oblique, nor the inferior rectus without the superior oblique. This, however, must not be interpreted as indicating that the paralysis is due to a lesion of the nervous

paths by which these muscles are linked together, since, as will be pointed out later, it is certainly mainly a mechanical effect of the exophthalmos. When the ophthalmoplegia is unilateral, elevation is the movement most often affected (Plate 22, Fig. 5) for in the 13 unilateral cases elevation was weak or paralysed in all, whereas abduction was affected in four cases and adduction and depression in one case only. Thus, if a single movement of one eye is affected alone, it is usually elevation. When both eyes exhibit ophthalmoplegia, however, abduction is the movement which suffers most often, for in the 18 bilateral cases abduction was affected 29 times, elevation 23 times, depression 16 times, and adduction 16 times. If the unilateral and bilateral cases are grouped together, it is found that elevation and abduction are affected with about equal frequency and about twice as often as depression and adduction, which are also affected with about equal frequency. All movements of both eyes were weak in six patients. The degree of weakness of an ocular movement is usually constant from one day to another and does not fluctuate, though a movement may gradually become weaker, or further movements may become involved as the exophthalmos increases. Not uncommonly patients say that the double vision is worse in the morning and improves somewhat as the day goes on. Bandaging the eye, if any backward pressure is exerted, tends to make the ophthalmoplegia temporarily worse.

*The eyelids.* Widening of the palpebral fissures with retraction of the upper lids is usually present both in unilateral and bilateral cases, but ptosis was present on both sides in five cases and on one side in three cases with bilateral ophthalmoplegia. In one case bilateral ptosis was the only ocular palsy present. In no case was the ptosis by any means complete. All possible combinations of lid retraction, ptosis and normality are encountered on the two sides. The oedema of the lids has already been described.

*The optic nerves.* Papilloedema, going on if unrelieved to optic atrophy and consequent blindness, has been described in a number of cases, usually those in which progressive exophthalmos followed thyroidectomy (Naffziger, 1931; Naffziger and Jones, 1932; Thomas and Woods, 1936; Ruedemann, 1937). In this series, however, papilloedema was noted in only one patient, one of the two post-operative cases. This man had two diopters of papilloedema in each eye, but vision was unimpaired.

*The central nervous system and the muscles.* In no case was there any clinical evidence of a lesion of the central nervous system. In every case the reactions of the pupils to light and accommodation were normal, in striking contrast to the external ophthalmoplegia. Abnormalities in the muscles other than the ocular muscles, were present in only one case (Plate 22, Fig. 6). This patient exhibited generalized muscular wasting and weakness with fibrillation, and diminution of the knee- and ankle-jerks and is fully reported by Starling, Darke, Hunt, and Brain (1938). The bodily musculature recovered completely after partial thyroidectomy. As

stated later, this generalized muscular wasting is regarded as a thyrotoxic myopathy which is rarely associated with exophthalmic ophthalmoplegia, and, since it may also occur in the absence of ophthalmoplegia, is probably of different aetiology. The cerebrospinal fluid in those cases in which it was examined was normal and the same is true of radiograms of the skull.

*General symptoms.* In contrast with the severity of the exophthalmos, the general symptoms of thyrotoxicosis were usually slight. In only six cases out of the 31 were they severe enough to necessitate admission to hospital on their account alone. The average patient made no complaint of palpitation, and little, if any, of nervousness. In fact the patient's placid appearance in spite of the exophthalmos was in striking contrast with the anxious expression of the typical patient with exophthalmic goitre. Loss of weight, if present, was usually slight, and was substantial in only five cases. The thyroid gland was visibly enlarged in five and appeared slightly enlarged on palpation in a further nine. In two of the remainder, partial thyroidectomy had already been carried out. The skin was usually warm and moist; tremor of the hands was noted in 17, but was rarely marked; the pulse-rate was usually below 100 and only one patient had auricular fibrillation. Facilities for investigating the basal metabolic rate were available in eight patients only. The maximum was +45 per cent. and the average for the eight was +25 per cent. Two were within normal limits. The blood-pressure was normal in all, save one who had a coincident hypertension. Diminished sugar tolerance and glycosuria were present in one. Cutaneous pigmentation has often been noted in exophthalmic ophthalmoplegia. Most frequently it took the form of small light-brown freckles scattered about the eyes. One patient, however, exhibited in addition a sheet of light yellowish pigmentation extending over both cheeks, and in another (Plate 22, Fig. 7) there were similar sheets of pigmentation symmetrically disposed over both sides of the face and neck and the dorsum of both forearms and hands. These areas were light yellowish brown in winter and became dark brown in summer. One male patient with unilateral exophthalmos and ophthalmoplegia exhibited on the same side as his exophthalmos slight enlargement of the breast which intermittently secreted a clear fluid. A female patient in whom the onset of the disorder was acute, and in whom both eyes were affected, complained of a feeling of painful congestion of both breasts.

*Course, prognosis, and results of treatment.* Two of the 31 patients of this series died, one from purulent pericarditis and the other from heart-failure associated with auricular fibrillation. Of the remaining 29, five have either been lost sight of or have not been observed long enough for an opinion to be formed as to the outcome. This leaves 24 patients, most of whom have been under observation for several years. In only three has there been a complete recovery from the ocular abnormalities with disappearance of both exophthalmos and ophthalmoplegia; 10, although more or less improved, still suffer from exophthalmos and ophthalmoplegia; 10 are in these respects

unchanged, and one has become worse. The chance of complete recovery of the eyes is thus very small. In almost all cases the exophthalmos and ophthalmoplegia having reached their maximum in a few months either remain stationary or partially subside, in either case leaving the patient with considerable disfigurement and double vision. One of my patients (Plate 22, Fig. 7) has attended Moorfields Hospital since the onset of his disorder in 1917, and as far as can be judged, the condition has been stationary for 20 years. Moore (1937) has reported a case in which the ophthalmoplegia persisted unaltered for 24 years. These figures show that treatment is on the whole ineffective. The usual medical measures employed in the treatment of hyperthyroidism have been quite valueless, no benefit having followed rest, sedatives, or iodine. Ovarian follicular hormone has also proved useless. Ruedemann (1937) recommends the administration of thyroid extract up to the limit of tolerance, but Thomas and Woods (1936) reported that thyroid extract was ineffective in five of their patients, and I have tried it in one case without benefit. X-ray treatment of both the thyroid gland and the pituitary fossa has been without result in my experience. Thyroidectomy has been carried out in six cases. In one it was done too recently for any conclusion to be drawn. Of the remaining five cases substantial improvement occurred in one case, though the double vision was not completely abolished. In three cases the condition of the eyes remained unchanged, and in the remaining one case both exophthalmos and ophthalmoplegia were slightly worse after the operation. Naffziger's operation consists of a decompression of the orbit after removal of its roof by a transfrontal approach. Naffziger himself reports a case in which the exophthalmometer reading diminished from 34 to 23 mm. after operation, with corresponding improvement in the range of movement of the eye and in vision. Professor Hugh Cairns carried out this operation on three patients in this series. In all three there was obviously a great increase in tension in the orbital contents, and on removing the roof of the orbit they bulged up. Following orbital decompression there was an immediate recession of the eye, but the ophthalmoplegia remained unchanged in one case and was only moderately benefited in the other two. It would appear that if this operation is to be of benefit it must be carried out early, as permanent changes in the extra-ocular muscles evidently occur rapidly, and decompression after this will not completely relieve the ophthalmoplegia. Papilloedema with deteriorating vision would obviously constitute an even more important indication for orbital decompression than exophthalmos and ophthalmoplegia, as also would threatened corneal ulceration.

#### *Pathology*

*The central nervous system.* The possibility that the ophthalmoplegia may be the result of changes in the central nervous system first requires consideration. There is no evidence that this is the case and much evidence

to the contrary. A few of the older writers have described lesions in the brain-stem in association with neurological complications of Graves' disease, but the clinical condition in such patients differs from exophthalmic ophthalmoplegia. For example, Kappis (1911) reported a patient with Graves' disease who had a unilateral paralysis of the glossopharyngeal and vagus nerves. At autopsy there was a focal lesion of the medulla, but since the patient had an irregular pulse and died of heart-failure this lesion was probably embolic. Heuer (1916) states that in four of six cases of bulbar paralysis associated with Graves' disease reported in the literature, definite lesions were present in the medulla, associated with extensive degeneration of fibre tracts. Heuer admits, however, that in the large majority of patients whom he describes as suffering from cerebral nerve disturbances in exophthalmic goitre, the palsies have affected chiefly the eye muscles, and, since in these cases the disorder is not usually fatal, pathological observations are lacking. In one such case, however, reported by Wedd and Permar (1928) the brain was thoroughly examined. Serial sections made from twenty-five areas on each side between the basal ganglia and the medulla showed no lesion. Further, there is ample evidence, described in the next section, of the presence of gross changes in the extra-ocular muscles which indicate a muscular disorder as the cause of the ophthalmoplegia. The available evidence, therefore, indicates that the ophthalmoplegia is not central in origin.

*The ocular muscles.* Most of the pathological observations hitherto made on the ocular muscles have been in cases of exophthalmic ophthalmoplegia in which this disorder has followed partial thyroidectomy. Burch (1929) described the ocular muscles as greatly enlarged, 1 to 3 cm. in thickness, and exhibiting degeneration, oedema, and infiltration with lymphocytes. Naffziger and Jones have reported four similar cases (Naffziger, 1931; Naffziger, 1933; Naffziger and Jones, 1932). These authors also state that 'grossly, the muscles are from three to eight times their normal size. Microscopic study shows oedema, round cell infiltration—often in a perivascular form—loss of muscle architecture, increase of fibrous tissue with areas of hyalinization, and fragmentation and destruction of muscle fibres.' Thomas and Woods (1936) have examined sections of the eye muscles of three patients exhibiting exophthalmos following thyroidectomy. In one case the muscles showed changes similar to those described by Naffziger, while in the two other cases the muscles appeared normal. Stallard (1936, 1937) has reported a case in which exophthalmic ophthalmoplegia developed spontaneously and not post-operatively. In this case 'the extra-ocular muscles were considerably enlarged, being five or six times their normal size and were pale and fusiform in shape. Histological examination of the piece of the inferior rectus muscle showed an interstitial fibrosis and chronic inflammatory round-cell infiltration. The muscle fibres exhibited no definite degenerative changes.' Stallard's patient shows that the same macroscopic and histological changes are present in the spontaneous as in the post-operative cases. Professor H. M. Turnbull has kindly made histological examinations of extra-ocular muscles from two

of my patients, and of the thyroid glands from six. His observations are summarized here and reported in full at the end of the paper.

*Case 1.* In this case the ocular muscles were examined *post mortem*. The bundles of muscles were separated farther than in control material, the interstitial tissue being torn. It was considered that the tearing was an artifact, but that it might possibly have been induced by oedema. In all muscles there were one or two perivascular areas of infiltration in which lymphocytes, a few monocytes, and occasional plasma cells were closely packed together. A lymphorrhage was found in a sternohyoid muscle also.

*Case 6.* The material in this case consisted of tissue removed from the orbit at operation. A portion of the levator palpebrae superioris was examined. The changes not present also in the control were recent haemorrhages accompanied by serous exudate, general oedema, and great enlargement of muscle fibres. The diameter of 100 muscle fibres was measured in the specimen and in a control. In the control the minimal and maximal diameters were 7 and 24  $\mu$ , the mean 14.6  $\mu$ , and the mode 15  $\mu$ . In the specimen the minimal and maximal diameters were 15 and 60  $\mu$ , the mean 30.8  $\mu$ , and the mode 25  $\mu$ . The muscle fibres in the specimen showed longitudinal and cross-striation, but the cross-striation was less distinct than in the control. In sections cut at the same thickness and stained synchronously most of the fibres in the specimen were stained less deeply than in the control, but some large fibres were stained as deeply. It was considered that the haemorrhages and serous exudate were due to the operative removal, but that it was unlikely that the general oedema, and most unlikely that the enlargement of the muscle fibres, was the result of operative interference. The nature of the changes in the muscle fibres was obscure.

*Orbital changes in a long-standing case.* Early fibrotic changes in the ocular muscles have already been described. The final state of the extra-ocular orbital tissues in one patient in whom exophthalmic ophthalmoplegia had been present for six and a half years was a condition of generalized fibrosis. The patient's right eye became painful and had to be enucleated. Mr. A. H. Briggs, who performed this operation, reported as follows: 'The tarsorrhaphy was divided under novocaine anaesthesia. The conjunctiva was found to be atrophic and very friable, and the globe was completely immobile. The eye could not be moved appreciably by means of forceps. Enucleation of the globe was carried out; this was rendered difficult by the complete immobility of the globe. The globe appeared to be completely anchored in the orbit by strands of dense fibrous tissue, and the extra-ocular muscles could only be identified with difficulty as thin fibrotic bands. The globe was eventually successfully enucleated. It was then found that there was a large old-standing hole in the lower lid, which was repaired. The tarsorrhaphy was sewn up again for cosmetic reasons.'

*The eye.* Only one eye from a patient with exophthalmic ophthalmoplegia has become available for examination. Its removal is described in the previous section. This eye was examined by Mr. Frank Law who

reported as follows: 'There is an extreme degree of degeneration of the cornea, doubtless due to exposure keratitis. The anterior chamber contains exudate, and there is a dense cellular deposit on the posterior corneal surface, though inflammatory changes in the anterior uveal tract are not now evident. The presence of posterior synechiae and a pupillary membrane confirm the suggestion, however, of past iridocyclitis. The condition of the retina is good, there being no more than the usual degree of peripheral cystic degeneration. The retinal blood-vessels show no pathological change. Though special staining methods were not adopted, there is no obvious pathological change in the optic nerve; in it the central vessels are cut in cross-section and appear normal.'

*The thyroid.* Sections from the thyroids of six patients have become available for examination. The thyroid of Case 1 was obtained *post mortem*. In Cases 2, 3, 4, and 5, sections were obtained from portions of the gland removed surgically, in the course of treatment for this disorder. In Case 6 exophthalmic ophthalmoplegia developed post-operatively and the sections were obtained from portions of the gland removed at operation for hyperthyroidism five and a half months before ophthalmoplegia appeared. Professor Turnbull has kindly examined the sections of the thyroid and has compared them with a control series of sections from fifty thyroid glands from patients with clinically typical Graves' disease. His findings are summarized here and reported in full at the end of the paper. In the section from Case 1 the changes found were typical of Graves' disease. In the sections from Cases 2, 3, 4, and 5 the histological changes were atypical. Professor Turnbull summarizes the changes by saying that in these four cases 'there is, in short, more evidence of colloid retention and less evidence of colloid secretion or transference than in goitres characteristic of Graves' disease. . . . It follows that it is not possible to say that the changes in the glands in Cases 2, 3, 4, and 5 are incompatible with Graves' disease. It is only possible to say that they correspond to findings that are unusual in Graves' disease and are of a kind that was found only in five out of a series of 50 glands.' Concerning the thyroid from Case 6, Professor Turnbull said: 'The picture differs in certain respects, for instance in the lack of uniformity of the affection of the lobules, from that which is characteristic of acute Graves' disease treated with iodine. A similar picture is, however, found in some examples of Graves' disease, and I should expect this gland to have been associated with definite signs of thyrotoxicosis.'

#### *Actiology*

*The causation of the ophthalmoplegia.* As we have already seen, there is no reason to attribute the ophthalmoplegia to a lesion of the central nervous system. It never corresponds in distribution with the effect of a lesion of one or more of the nerves supplying the ocular muscles, save in those rare cases in which the external rectus is paralysed alone, and these cases do not

make it possible to distinguish between a lesion of the nerve and the muscle.

✓ The pathological evidence already quoted makes it clear that the ophthalmoplegia is often associated with gross lesions of the muscles, and all the evidence points to its being due to a disorder of function of the muscles themselves. It must not be assumed, however, that the histological changes found in the muscles are themselves the cause of the disorder of function. The muscles in some cases appear to be histologically normal. Perivascular infiltration of the muscles with lymphocytes has been described by Dudgeon and Urquhart (1926) in many of the somatic muscles in exophthalmic goitre. The significance of these infiltrations is unknown, but it is unlikely that they can be the cause of muscular paralysis. The severe oedema of the ocular muscles, the dense infiltration with lymphocytes, and the fibrosis described by several authors seem to be characteristic of an advanced stage of the disorder, and while no doubt contributing to the impairment of muscular contraction, are probably not its primary cause. The ophthalmoplegia seems invariably to be closely linked with the exophthalmos, being in general proportional to it. ✓ Thus when the exophthalmos is unilateral so too is the ophthalmoplegia. When the exophthalmos is asymmetrical the ophthalmoplegia either is limited to the more protruding eye or is more severe and extensive upon the side of the greater exophthalmos. Conversely, if the orbit be decompressed the ophthalmoplegia diminishes *pari passu* with the diminution in the exophthalmos.

In order to understand the association between exophthalmos and ophthalmoplegia it is necessary to bear in mind certain features of the anatomy of the orbit. The extra-ocular muscles arise from a bony attachment at the apex of the orbit and, with the exception of the levator palpebrae superioris, are inserted anteriorly into the globe of the eye. The orbital fascia which surrounds the globe in front passes backwards to invest the ocular muscles on both their surfaces and to blend with the lateral expansion of the muscle sheaths. Thus the ocular muscles with their sheaths and the orbital fascia form a cone, the apex of which is anchored to the orbit posteriorly and the base of which is formed by the eye. This cone is packed with fat. ✓ There is reason to think that the ophthalmoplegia is due in the first instance to a rise of pressure within the cone of muscles, and that the same rise of pressure causes the exophthalmos. Charpy (1931) has shown experimentally that injections of fluid into the central part of the orbital fat within the cone of muscles causes both exophthalmos and immobility of the eye. ✓ Observations made at operation on the orbit in cases of exophthalmic ophthalmoplegia have shown that there is a marked rise of tension within the orbital fascia and that as soon as this is incised the fat within bulges out. The diminution in the exophthalmos and in the ophthalmoplegia which follows this operation is evidently the result of the reduction of the tension. Further, the ophthalmoplegia may be temporarily increased by bandaging a firm pad over the eye. Evidently backward pressure on the globe increases the tension of the ocular muscles. Lastly, this hypothesis also explains the relative rarity of paralysis of the levator palpebrae superioris in exophthalmic

ophthalmoplegia, for this ocular muscle is unique in that its anterior insertion into the upper lid is not fixed, but mobile. Consequently the rise of tension within the cone of muscles does not stretch the levator palpebrae as it does the other ocular muscles, for when the levator is pushed upwards the upper lid becomes retracted and the length of the muscle remains the same. This may not be the only cause of retraction of the upper lid, which has also been attributed to contraction of the smooth muscle of the lid, but it is probably an important factor in causing lid retraction when ophthalmoplegia is present.

It is likely that at first the rise of tension within the cone of muscles interferes with movement of the eye mechanically, since, as has already been pointed out, the ophthalmoplegia is often limited to one direction in a single plane, for example vertically upwards. If the rise of tension increases, other factors become operative as is shown by the great increase in size of the ocular muscles, which is probably due to oedema. It seems likely that this is due to a peculiarity of the venous drainage of the orbit. Both the superior and the inferior ophthalmic veins run for a part of their course within the cone of muscles, emerging posteriorly to enter the cavernous sinus. In their passage within the cone of muscles these veins receive blood from the muscles themselves. Consequently if the tension within the cone of muscles rises above the venous blood-pressure, the veins will become compressed and oedema of the muscles will result. This will tend to raise the tension still further and to increase the exophthalmos, and so to produce a vicious circle comparable with those which occur within the cranial cavity in increased intracranial pressure. The possibility must be considered that the rise of tension within the cone of muscles may cause muscular weakness by compressing the nerves supplying them. This, however, seems unlikely since the nerve to the levator palpebrae superioris would appear to be especially vulnerable in this respect because it passes through the superior rectus muscle on its way to the levator. Yet although the superior rectus is frequently weak or paralysed, the levator is rarely affected. For a similar reason weakness of the superior rectus can hardly be due to compression of the superior division of the third nerve which supplies both this muscle and the levator.

It is also necessary to consider whether the ophthalmoplegia may be due in part to the direct action upon the ocular muscles of a toxin, possibly an excessive secretion of the thyroid. As will be shown later, there is evidence that such a toxic myopathy is sometimes present in hyperthyroidism. In such cases the toxin may well affect the ocular muscles as well as other muscles of the body. Nevertheless, such a myopathy was present in only one of the 31 patients with exophthalmic ophthalmoplegia, and on the other hand I have seen three patients with thyrotoxic myopathy without ophthalmoplegia. It is unlikely, therefore, that such a toxic action upon the muscles plays any important part in the aetiology of the ophthalmoplegia in most cases. It is natural to inquire why, if the ophthalmoplegia is the result of the exophthalmos, it is not part of the typical clinical picture of exophthalmic goitre. This is in part explained by the fact already mentioned that in exophthalmic

ophthalmoplegia the exophthalmos is usually much greater than in exophthalmic goitre. A second factor which appears to be of importance is the rate at which the exophthalmos develops. The more rapidly exophthalmos develops, the more likely it is that ophthalmoplegia will occur, and in exophthalmic ophthalmoplegia protrusion of the eyes commonly develops not only to a much greater extent, but also much more rapidly than in exophthalmic goitre.

*The causation of the exophthalmos.* The proximate cause of the exophthalmos in exophthalmic goitre is still unknown. Numerous explanatory hypotheses have been put forward. Since the clinical observation of the group of patients who are the subject of this paper throws no more light upon this problem than is contained in the previous section it will not be further discussed here. The study of exophthalmic ophthalmoplegia, however, does illuminate the remoter causes of exophthalmos, in particular the rôle of the thyroid and of other factors in its aetiology.

*The rôle of the thyroid.* The association of exophthalmos with the general symptoms of hyperthyroidism in exophthalmic goitre led, perhaps naturally, to the belief that the hyperthyroidism was the cause of the exophthalmos. During recent years, however, evidence has accumulated which renders it unlikely that this view is correct. The following are the facts which must be taken into consideration in assessing the rôle of the thyroid in the production of exophthalmos. A review of the literature (Brain, 1936) shows that the administration of thyroid extract or of thyroxine only very rarely, either in man or in animals, produces exophthalmos. I was able to find only 18 reported cases of this sequence of events in man, to which I added one further case. These exceptional cases exhibit two points of interest. Of the 19 patients, 11 suffered from obesity, six from myxoedema, and two from goitre. It is noteworthy that the only animals in which exophthalmos followed the administration of thyroid extract were thyroidectomized rabbits (Kunde, 1927). Secondly, in almost all the patients in whom exophthalmos followed the administration of thyroid extract, a condition indistinguishable from exophthalmic goitre developed, and in some cases necessitated thyroidectomy. Consequently it cannot be inferred that the exophthalmos in these patients was the direct result of the administration of the thyroid extract. It is not uncommon for the general symptoms of hyperthyroidism to occur even in a severe form without exophthalmos, as in the condition called 'toxic adenoma of the thyroid' or 'secondary hyperthyroidism'. Even in exophthalmic goitre the exophthalmos may precede the general symptoms of hyperthyroidism and usually long outlasts them, when they subside either spontaneously or after subtotal thyroidectomy. Marine and his collaborators (Marine, Spence, and Cipra, 1931; Marine and Rosen, 1932, 1934; Marine, Rosen, and Cipra, 1932) who succeeded in producing exophthalmos in rabbits by means of methyl cyanide and by the thyrotropic hormone of the pituitary, found that both these substances produced exophthalmos more readily and to a greater

extent in animals from which the thyroid had previously been removed than in normal rabbits. Friedgood (1934), working with the thyrotropic hormone of the pituitary, concluded that the exophthalmos which resulted from administration of this extract was produced independently of the thyroid secretion and occurred more readily with the animal in a hypothyroid state than when it was hyperthyroidic. Smelser (1937), by administering the thyrotropic hormone of the pituitary to thyroidectomized guinea-pigs, has produced exophthalmos which persisted after death in 47 out of 50 animals. In conformity with the foregoing observations, I have noted that in exophthalmic ophthalmoplegia the exophthalmos bears no constant relation to the presence of hyperthyroidism. In exophthalmic ophthalmoplegia the exophthalmos may be associated with marked general symptoms of hyperthyroidism, though this is uncommon. Usually such general symptoms are slight and they may be absent. In some cases in which exophthalmic ophthalmoplegia develops after subtotal thyroidectomy the patient is in a state of post-operative myxoedema as, for example, in three patients in the series reported by Thomas and Woods (1936). If subtotal thyroidectomy be performed upon a patient suffering from exophthalmic ophthalmoplegia, the exophthalmos may either diminish, remain stationary, or even increase. These facts seem to show that neither in exophthalmic goitre nor in exophthalmic ophthalmoplegia is the exophthalmos primarily the result of hyperthyroidism. Nevertheless, the common observation that the exophthalmos usually diminishes after subtotal thyroidectomy in patients with exophthalmic goitre seems to indicate that the thyroid is a contributory factor. In view of what has been said in a previous section with regard to the circulatory factor in the production of exophthalmos, it seems likely that the vasodilator effect of thyroxine would enhance an exophthalmos set up by some other factor, and that the improvement which follows thyroidectomy in exophthalmic goitre is the result of the removal of this contributory vascular factor due to thyroid secretion. Some writers have attributed the occurrence of progressive exophthalmos following thyroidectomy to myxoedema. This explanation is unacceptable for several reasons. Exophthalmos plays no part in the symptomatology of spontaneously arising myxoedema. Moreover, although exophthalmic ophthalmoplegia may be associated with post-operative myxoedema it may, when it arises spontaneously, also be associated with slight or severe hyperthyroidism.

*The rôle of the thyrotropic hormone of the pituitary.* The discovery that the anterior lobe of the pituitary contains a hormone which stimulates the thyroid and produces in animals the symptoms of Graves' disease, including exophthalmos, promises to throw fresh light on the aetiology of this disease and in particular on the pathogenesis of the exophthalmos. As described in the previous section, numerous workers have now demonstrated that whereas the thyrotropic hormone induces in the intact animal both exophthalmos and the general symptoms of thyrotoxicosis, it will still induce the

exophthalmos in thyroidectomized animals, if anything more readily than in intact animals. Moreover, in intact animals the exophthalmos persists and may become more evident when the animal has passed into a hypothyroid state as a result of the thyroid having become refractory to the thyrotropic hormone. The results of the administration of the thyrotropic hormone to animals soon suggested that exophthalmic goitre might be due to prolonged stimulation of the thyroid by this hormone. If this were proved, the evidence just cited would suggest that the exophthalmos is primarily the result of the action of the thyrotropic hormone. The hypothesis, however, encountered two difficulties. It was found that repeated doses of the thyrotropic hormone did not produce a continuous stimulation of the thyroid, since the gland rapidly became refractory and the animal might even pass into a hypothyroid condition. Collip and Anderson (1934) showed that this development of a refractory state was due to the production by the organism of an anti-thyrotropic substance. Loeser (1937), however, has recently shown that the refractory state does not develop if the animal is given increasing instead of constant doses of the thyrotropic hormone. In this way it is possible to induce in an animal a fatal degree of hyperthyroidism. Loeser considers that at least two ways are conceivable by which a continual state of hyperthyroidism may be produced in man, firstly by a continual stimulation of thyroid activity by the thyrotropic hormone in spite of the existence of normal conditions for the production of the anti-thyrotropic principle, and, secondly, by the failure of this protective function in the presence of a constant or increasing animation of thyroid activity. The second difficulty in the way of accepting the pituitary origin of exophthalmic goitre is found in the observations of those workers who have sought for the thyrotropic hormone in the blood and urine of patients suffering from thyroid disorders. Several workers have failed to find evidence for the production of an excessive amount of thyrotropic hormone in exophthalmic goitre. Recently Hertz and Oastler (1936) have found that whereas the blood-serum and urine from myxoedematous patients contain appreciable quantities of thyrotropic material, none of the thyroid stimulating factor could be demonstrated in the body fluids of either thyrotoxic or normal individuals. Antognetti and Geriola (1936) also failed to demonstrate the thyrotropic hormone in the urine of thyrotoxic subjects. Dr. A. W. Spence obtained negative results with the blood-serum of the patient with exophthalmic ophthalmoplegia illustrated on Plate 22, Fig. 4. Too much stress must not be laid upon these observations, however, especially in view of the suggestion of Marine (1935) and Loeser (1937) that exophthalmic goitre may be due not to an excessive production of the thyrotropic hormone, but to a break-down in the protective action of the anti-thyrotropic principle. It is clear that there is still much to be learned, not only about the action of the thyrotropic hormone, but also about the mutual relations of the pituitary and the thyroid. In the present state of our knowledge the most that can be said is that the

exophthalmos of Graves' disease is almost certainly not primarily produced by thyroxine, but is the result of some other factor which may well prove to be the thyrotropic hormone of the pituitary. Such a hypothesis illuminates many of the clinical features of exophthalmic ophthalmoplegia. The prominence of the ocular symptoms and usual slightness of the general symptoms of hyperthyroidism in this condition recall the condition of the experimental animal in the refractory phase after the administration of thyrotropic hormone, and there is a considerable resemblance between the histological picture found in the thyroid in four out of five of my cases of spontaneous exophthalmic ophthalmoplegia and that found in the guinea-pig's thyroid after the prolonged administration of thyrotropic hormone. The hypothesis also affords an explanation of the development of progressive exophthalmos in thyrotoxic patients, for Zeckwer (1936) has shown that, following thyrotoxicosis in animals, the total amount of thyrotropic hormone in the pituitary is larger than in controls. There is thus evidence that thyroidectomy causes an increased production of the thyrotropic hormone. This is probably the explanation of the increased ease with which exophthalmos is produced experimentally by the administration of the thyrotropic hormone after thyroidectomy and may also explain progressive post-operative exophthalmos in man. It is tempting to ascribe the occasional occurrence of exophthalmic goitre as a complication of acromegaly to the excessive production of thyrotropic hormone by the adenoma of the anterior lobe of the pituitary.

The observations of Smelser (1937) are most significant. He found that the exophthalmos induced in thyroidectomized guinea-pigs by the thyrotropic hormone of the pituitary was due to increase in bulk of the orbital contents. The retrobulbar tissue of the exophthalmic animals was 34 per cent. greater than that of controls. The increase of weight was due to oedema of the orbital fat and extra-ocular muscles, which showed histological changes similar to those already described as characteristic of exophthalmic ophthalmoplegia in man. Smelser's work makes it highly probable that the orbital changes in exophthalmic ophthalmoplegia are produced by the thyrotropic hormone of the pituitary.

#### *Other Muscular Disorders associated with Thyrotoxicosis*

Allusions have already been made to a condition which has been termed thyrotoxic myopathy. It is not proposed to consider here at length the varieties of muscular disorder which may be associated with thyrotoxicosis, but only to discuss them in so far as they are of interest in relation to exophthalmic ophthalmoplegia. That thyrotoxicosis influences muscular function is evident histologically from the observation of Dudgeon and Urquhart (1928) that lymphorrhages are often to be found, as in my Case 1, in the somatic muscles in Graves' disease; biochemically from the abnormal excretion of creatine in that disorder; and clinically from the well-known

fatiguability of patients with exophthalmic goitre. Rarely the muscle disorder is so marked as to become a prominent symptom. The following clinical varieties of this may be recognized: (1) acute thyrotoxic myopathy, (2) chronic thyrotoxic myopathy, (3) thyrotoxic periodic paralysis, and (4) myasthenia gravis associated with thyrotoxicosis.

*Acute thyrotoxic myopathy.* This condition is very rare and I have never seen an example of it. Instances have been reported by Sattler (1909), Kappis (1910), and Heuer (1916). In addition to the general symptoms of a severe thyrotoxicosis, exophthalmos, and ophthalmoplegia these patients exhibit a rapidly developing bulbar palsy, with paralysis of the muscles of mastication, expression, and deglutition and generalized weakness of the limbs. Heuer believed that not more than 10 cases of this kind had been reported up to 1916. Death always occurs, usually within a week or two of the onset of the bulbar symptoms.

*Chronic thyrotoxic myopathy.* In this disorder muscular wasting and weakness develop insidiously in the course of thyrotoxicosis. One example is included in the series of patients reported in this paper, since ophthalmoplegia was also present. More often it is absent. Chronic bulbar palsy is also rare, but was present in Rennie's (1908, 1919) case. As a rule the muscular weakness and wasting are limited to the muscles of the trunk and limbs, their distribution is symmetrical, and the muscles of the shoulder girdle and pelvic girdle are often more conspicuously affected than the peripheral muscles of the limbs. Coarse muscular fibrillation may be seen, and the tendon reflexes are diminished or lost. In distinction from both myasthenia gravis and progressive muscular atrophy, recovery from the thyrotoxicosis is followed by complete and permanent recovery from the myopathy (Starling, Darke, Hunt, and Brain, 1938).

*Thyrotoxic periodic paralysis.* The occurrence in the course of thyrotoxicosis of symptoms indistinguishable from those of periodic paralysis has been reported. Dunlap and Kepler (1931) published four cases of periodic paralysis associated with exophthalmic goitre, in all of which the paralysis disappeared on treatment of the thyroid disorder. Morrison and Levy (1932) have reported a further case which was relieved by operation on the thyroid. I have seen one similar case, a man aged 53, whom I saw in two attacks of periodic paralysis, one lasting twelve hours and one twenty-four hours. He had an adenomatous goitre and a basal metabolic rate of +42.5 per cent. Subtotal thyroidectomy was followed by complete relief of his muscular symptoms, and when seen three years after the operation he had remained well. All the evidence points to thyrotoxic myopathy and thyrotoxic periodic paralysis, being due to the direct effect of thyrotoxicosis upon the muscular function. Shorr, Richardson, and Wolff (1933*a*, 1933*b*) believe that the muscular wasting in Graves' disease is the result of a reparable impairment of the phospho-creatine mechanism and is of the nature of an acute muscular dystrophy, similar in many respects to the disturbance of progressive muscular dystrophy.

*Myasthenia gravis associated with thyrotoxicosis.* Confusion has arisen in the past from a failure to distinguish between exophthalmic ophthalmoplegia and myasthenia gravis complicating thyrotoxicosis. Thus Cohen and King (1932) in their review of 'The Relation of Myasthenia Gravis and Exophthalmic Goitre' failed to distinguish between these two conditions, and Rennie (1908, 1919) reported as an example of 'exophthalmic goitre combined with myasthenia gravis' a patient who appears to have been suffering from exophthalmic ophthalmoplegia associated with thyrotoxic myopathy. Nevertheless, the association of myasthenia gravis with thyrotoxicosis unquestionably occurs, and I have recently had an opportunity of seeing an example of it, reported by Fraser (1937). The distinction between exophthalmic ophthalmoplegia and myasthenia gravis complicating exophthalmic goitre depends upon a number of factors. (1) In most cases of exophthalmic ophthalmoplegia the paralysis is limited to the external ocular muscles, and of these the levator palpebrae superioris often escapes. In myasthenia, on the other hand, ptosis due to paresis of the levator is common, and it is rare for the external ocular muscles to be affected without simultaneous involvement of other muscles, especially the orbiculares oculi. (2) Patients with exophthalmic ophthalmoplegia do not exhibit the fatiguability of the affected muscles which is characteristic of myasthenia, and unlike myasthenic patients are not worse towards the end of the day. (3) The course of exophthalmic ophthalmoplegia is quite unlike that of myasthenia gravis, since when the exophthalmos and ophthalmoplegia have attained their maximum there is usually some spontaneous improvement and the condition then becomes arrested, leaving the patient with some ophthalmoplegia and protrusion of the eyes, but otherwise well. Neither the relapses and remissions nor the generally downhill course characteristic of myasthenia are observed. (4) Perhaps the most valuable distinction is the difference in the response to prostigmin. Thus Fraser's patient, who was suffering from myasthenia gravis complicating exophthalmic goitre, temporarily lost her ophthalmoplegia completely while under the influence of prostigmin. In another of his patients, however, in whom there was ophthalmoplegia associated with thyrotoxicosis, the ophthalmoplegia completely failed to respond to prostigmin. Fraser offers two possible explanations of this difference, either that the pathology of the two conditions is different or that in the second case the disease had progressed to a stage in which the muscle was no longer capable of responding to prostigmin. I have given full doses of prostigmin to six of my patients in this series; in none of them did it produce the slightest improvement in the ocular movements. Three of these patients were tested within three months of the onset of their ophthalmoplegia. The clinical differences, together with the difference to the response to prostigmin, seem to afford conclusive evidence that exophthalmic ophthalmoplegia and myasthenia gravis complicating exophthalmic goitre are nosologically distinct.

*Summary*

1. This paper is an analysis of 31 examples of a syndrome characterized by exophthalmos and ophthalmoplegia, for which the name 'exophthalmic ophthalmoplegia' is proposed.

2. Exophthalmic ophthalmoplegia may arise spontaneously, in which case it is associated with general symptoms of thyrotoxicosis which are usually slight. It may also occur after subtotal thyroidectomy, when the patient's basal metabolic rate is normal or subnormal.

3. Thyrotoxicosis therefore plays no essential part in the aetiology of exophthalmic ophthalmoplegia which, for this reason and also by its age and sex incidence, is distinguished from exophthalmic goitre.

4. The clinical features of the disorder and pathological changes in the orbit and the thyroid glands are described.

5. Its aetiology is discussed with special reference to the rôle of the thyroid and of the thyrotropic hormone of the pituitary.

6. The exophthalmos is attributed to a factor other than thyroxin, and the ophthalmoplegia to the mechanical effect of the intra-orbital tension upon the ocular muscles.

7. Exophthalmic ophthalmoplegia is thus differentiated from the thyrotoxic myopathies and from myasthenia gravis complicating exophthalmic goitre.

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## APPENDIX

## PATHOLOGICAL REPORT BY HUBERT M. TURNBULL

*Case 1.* F. B. Female, aged 34. Summary of necropsy, P.M. 736/1914. Fibrino-purulent pneumococcal pericarditis. Acolloid goitre. Exophthalmos. Lymphorrhages in ocular muscles and sternohyoid. Large glandular thymus. Hypertrophy of faucial ( $7 \times 3.5 \times 3$  cm.) and lingual tonsils. No enlargement of lymphatic glands. Marked atrophy of Peyer's patches. Follicular cysts in atrophic ovaries. Diffuse engorgement of pancreas, intestines and liver. Engorgement, mucous catarrh, and submucous haemorrhages in stomach. Inflamed spleen. Muco-purulent bronchiectasis in fibrotic tuberculous scar on inner aspect of apex of right lung. Dense adhesion between scarred area

and trachea. A few fibrous adhesions over remainder of upper lobe of right lung. Epidermal remnants in pars tuberalis of pituitary body. Thick secretion in ducts of breasts. Abundant adipose tissue on chest (0.7 cm. deep), abdomen (2.5 cm. deep), and legs; arms wasted. Weights: body 36.6 kg. (length 1.6 m.); brain 1,318.3 gm.; liver 1,190.7 gm.; heart 304.8 gm.; kidneys 304.8 gm.; spleen 311.8 gm.; thymus 66 gm.; suprarenal bodies 18 gm.

*Macroscopic examination.* The lateral lobes of the *thyroid gland* measured  $7 \times 3.5 \times 3$  cm., and the isthmus was 3 cm. wide, 5 cm. high, and 2.2 cm. thick. A pyriform lobe extended from the isthmus to the hyoid bone. The cut surface everywhere was lobulated, of a pale purplish-brown and of the fleshy appearance of a pancreas.

*Microscopic examination.* (Plate 23, Fig. 8). The right and left lobes of the *thyroid gland* are divided by narrow fibrous septa into lobules of which many show a considerable loss of angularity. The acini in each lobule vary greatly in size. In general, large, sometimes very large, acini, with a wide lumen and an outline that is usually papillated or crenated, are conspicuous in a background of acini of small and intermediate size. A few acini are partly or completely filled with a homogeneous or vesiculated, faintly-stained coagulum that resembles serum rather than colloid; a few others contain threads or small spherical droplets of faintly stained coagulum. Most acini contain little or no coagulum. Numerous acini contain rounded desquamated epithelial cells. Most of the acini are lined with columnar cells, which are finely or, more often, coarsely vacuolated, have basal nuclei, and usually expand towards their free ends, often having bulbous extremities. Other acini are lined with spherical vacuolated cells, whose nucleus is nearer the base. Occasionally the cells are piled up locally into several layers so as to form cellular papillae. Among the epithelial cells are a few giant examples with single giant nuclei. There is no lymphocytic infiltration. The right and left lobes of the *thymus* consist of large lobules which show an abundant medulla and well-developed cortex and are separated by narrow septa. All the *muscles of the eye*, with the exception of the inferior oblique, were taken for examination from one or other side. The bundles of muscle-fibres are separated farther than in control material, the interstitial tissue being torn. The tearing is obviously an artifact, but it may possibly have been induced by oedema. In all muscles there are one or two small perivascular areas of infiltration in which lymphocytes, a few monocytes, and occasional plasma cells are closely packed together (Plate 21, Fig. 2). Occasionally also a small number of lymphocytes lie immediately outside a capillary. Single lymphocytes or monocytes are also present here and there in the interstitial tissue. In Jenner's stain granular leucocytes are confined to the vessels. The left levator palpebrae superioris is similarly affected. In the muscle-fibres longitudinal and cross-striation is distinct (Plate 21, Fig. 3); there are no abnormalities other than artifacts that are seen also in the controls. There is no increase of interstitial tissue. *Skeletal muscles.* In a sternohyoid muscle there is one small mass of lymphocytes round capillaries which lie

beside a nerve. A thyrohyoid muscle, the tongue, and the pharynx are free from such infiltration. No other muscles were examined.

*Case 2.* D. B. Female, aged 34. The specimen (S.D. 2641/1933) was the right half of the thyroid gland removed by operation.

*Macroscopic examination.* The specimen, received in formaldehyde solution, was the right lobe measuring  $3.5 \times 2.5 \times 1.2$  cm. and an attached portion of isthmus measuring 1.8 cm. long, 2.5 cm. high, and 1 cm. thick. The cut surface was in general soft, granular, pale pinkish-brown and glistening, and showed a few colloid cysts up to 0.15 cm. in diameter.

*Microscopic examination.* (Plate 23, Fig. 9). Two complete longitudinal sections of the lobe were embedded in paraffin. Their appearances are similar. Most of the lobules are considerably rounded. There is considerable fibrotic thickening of many of the interlobular septa. Many septa contain within defined spaces lakes of a coagulum which resembles colloid; others have their collagen fibres dissociated by similar coagulum. In each lobule most of the acini are large or very large and are filled with colloid, but between them here and there are small groups of small acini, some of which contain little or no colloid. The large acini are usually sub-angular or rounded. Several, however, are of irregular or crenated outline; a few show papillary projections, and a very few resemble dilated tubules. One or two rounded groups of acini of exceptional size correspond to the colloid cysts seen with the naked eye. The staining of the colloid varies, but is in general deep. It is specially deep in the groups of exceptionally large acini. Rarely, a few small vacuoles lie in the periphery of the colloid. Spheres of more deeply eosinophil coagulum opposite the epithelium are very rarely present. The colloid very seldom contains desquamated epithelial cells. The large acini are lined for the most part with slightly flattened cubical cells or greatly flattened cells, which have a central nucleus and little cytoplasm. The cytoplasm shows little vacuolation, appears dense, and is sharply defined towards the lumen. But not only are both these types of epithelium frequently present in the same acinus, but part of the lining consists often of larger, perfectly cubical cells with more abundant, more vacuolated cytoplasm or even of similar columnar cells with basal nuclei. It is opposite these larger cells that vacuoles are seen in the colloid. Some of the small acini are rounded vesicles very similar to the large, but the lining consists much more often of the larger cubical cells, while the colloid is often vacuolated and less deeply stained. Other small acini have a narrow lumen and are either rounded or elongated, or frankly tubular. Their epithelium is cubical or more often columnar, and is vacuolated; it is sometimes very ill-defined internally. Their lumina are empty or contain a little vacuolated pale coagulum. Transition forms between the large and small acini are obvious. There is no lymphocytic infiltration.

*Case 3.* A. L. Male, aged 33. The specimen (S.D. 936/1934) was the right lobe of the thyroid gland removed by operation.

*Macroscopic examination.* The specimen was received in formaldehyde solution. It had the shape of a complete lobe and measured  $7.5 \times 5.5 \times 2.5$  cm.

The outer surface was smooth, except near the posterior border, where some nodules, up to 1.5 cm. in diameter, projected. The cut surface was divided by white trabeculae, for the most part very delicate, into lobules of firm, pinkish-grey, glistening tissue.

*Microscopic examination.* (Plate 23, Fig. 10.) Two portions were embedded in paraffin. Loss of angularity of the lobules varies, but is in general considerable. There is slight thickening of the interlobular septa; thickening of the intralobular interstitial tissue is considerable. Most of the area of the sections is occupied by colloid acini which are large, but in general much smaller than in Case 2. All lobules contain also, however, areas of small acini in which there is rarely colloid. These areas appear very cellular. They vary in size and occupy relatively little of the total cut surface, but they are numerous and some are very large. They are much more conspicuous than the areas of small acini in Case 2. The large colloid acini are almost all sub-angular or rounded. A very few are branched or crenated. One or two show a papillary indentation. The colloid is moderately deeply stained. The epithelium consists usually of slightly flattened cubical cells or greatly flattened cells, though the latter seldom occupy the whole circumference. Many acini, however, are lined with cubical cells of moderate size; others, often in groups, are lined with large cubical or short columnar cells. These large cells are coarsely vacuolated, and a zone of vacuoles often lies in the colloid opposite their free extremities. Occasionally a few deeply eosinophil spheres lie opposite them. In the areas occupied by small acini lie a very few acini of considerable size. They are lined with large cubical or short columnar cells with an abundant, greatly vacuolated cytoplasm, and they are filled with desquamated epithelium, amongst which a multinuclear giant cell is sometimes present. The other acini are small. A very few are rounded vesicles filled with a colloid stained more deeply than elsewhere. The most numerous are small acini with a narrow lumen, and the majority are of tubular form. They are lined with similar large, vacuolated, cubical or short columnar cells. These sometimes have no internal definition, but blend with a vacuolated central area. Usually, however, they are sharply defined internally. The lumen is empty or contains a little greatly vacuolated faintly stained coagulum, or desquamated epithelial cells, or epithelial cells and faintly stained coagulum. Rarely the acini show no lumen or central vacuolated area and appear to form solid processes. The areas containing these small acini are frequently infiltrated with lymphocytes. Often the lymphocytic infiltration is great, and forms a conspicuous lymphoid nodule while the acini are reduced to a few in the margin. Where the lymphoid infiltration is absent or scanty, there are many collagen fibres between the acini, but where it is great and forms nodules collagen fibres are not seen.

*Case 4.* M. R. Female, aged 68. (Plate 22, Fig. 5.) The specimen is a section, stained with haematoxylin and eosin, received from another hospital.

*Microscopic examination.* (Plate 23, Fig. 11.) Many of the lobules are relatively small and angular, while other lobules or groups of lobules are so greatly enlarged and rounded that they form adenoma-like nodules to the naked eye. The appearances are of a nodular goitre. The smaller lobules vary, however, in size and form transitions to the larger; further, the changes they show differ from those in the larger in degree rather than kind. Apart from the variation in the size of the lobules, the changes are very similar to those in Case 3. The relative amount of tissue occupied by small acini is, however, greater. The stain is not suitable for the estimation of fibrosis. The interlobular septa appear to be delicate and no increase of intralobular interstitial tissue can be recognized. In the centre of the largest nodule the stroma is so oedematous that the acini appear to lie widely separated in a clear space crossed by a few poorly-stained fibrils. Most of the large lobules contain numerous large or very large acini filled with colloid. These are usually subangular or round. Elongated pyriform acini are fairly numerous. Acini with irregular outline are relatively rare, but are more numerous than in Case 3. The colloid is stained sometimes deeply, but more often somewhat lightly. There is one group of very large, elongated acini of very irregular outline, which are empty except for some pale coagulum in a single bay. The acini are lined usually with slightly or greatly flattened cubical cells that have little cytoplasm, occasionally with plump cubical cells that have more abundant cytoplasm. The lobules of small and intermediate size differ in that their larger acini are not so large, are lined with plump cubical cells, and more often contain a colloid which is very pale. Sometimes, indeed, the colloid is scanty or absent. The amount of tissue composed of small acini varies greatly in both large and small lobules. In general it is more abundant than in Case 3. It tends to lie particularly in the periphery of the lobules. In one large rounded lobule which forms a nodule (Plate 23, Fig. 11) it is very abundant, the larger acini being sparse and smaller than in the other nodules. In several also of the smaller lobules it is in conspicuous excess of the large acini, although these may be very large. Most of the small acini are round, oval, tubular, or irregularly shaped acini in which the lumen is narrow or absent. They are lined with large cubical or short columnar cells which have an abundant finely vesicular or spongy cytoplasm and are usually ill defined towards the lumen. Occasionally there is a conspicuous giant nucleus in one or more of the cells. Where a lumen is absent, the cytoplasm of the cells fuses in the centre. When a lumen is present it is empty, or contains a few droplets or threads of pale coagulum. Occasionally the lumen contains one or two desquamated cells. Transitions are found to a few wider acini which usually contain a pale, vacuolated coagulum, but occasionally are filled with desquamated epithelium. The pale coagulum frequently contains more deeply stained spheres. A few small vesicles filled with deeply stained colloid also occur. The areas of small acini are often associated with lymphocytic infiltration. This frequently forms large, focal, dense, nodular aggregations.

*Case 5.* R. C. Male, aged 42. (Plate 22, Fig. 6.) The specimen consists of two similar sections, both stained with haematoxylin and eosin, received from another hospital.

*Microscopic examination.* The amount of tissue is small. The sections are greatly shrunken, extensively torn in cutting, thick, and very heavily stained. It is only possible, therefore, to describe the grosser features with any certainty. The sections include one outer surface of the gland. At the surface are a few small lobular groups of acini embedded in abundant fibrous tissue. Beneath this the lobules vary greatly in size, but most are large and rounded. Between them there is usually a conspicuous excess of fibrous tissue, in which lie small lobules or groups of acini. The gland in consequence has a somewhat nodular appearance. By far the most acini contain colloid. Such acini are generally large. They are often very large, the largest lying in the largest lobules. Most are rounded. A few have a slightly sinuous outline or have a papillary projection from one wall. It is impossible to be certain of the shape of many of the largest owing to tearing of their walls. Small round, oval, or tubular acini containing little or no colloid, and occasionally filled with desquamated epithelium, are relatively rare and inconspicuous. They are very sparse in the largest lobules, but a few are usually present, particularly in the peripheries. They are more numerous in the lobules of intermediate and small size. There are several large nodular areas of lymphocytic infiltration. The relative amount of small acini without colloid to large colloid vesicles appears to be greater than in Case 2 and less than in Cases 3 and 4.

#### *Remarks.*

*Thyroid glands.* I was asked to determine whether the thyroid glands in these five cases showed the histological changes found in Graves' disease. There is much variety in the histological changes in the thyroid gland in cases diagnosed clinically as Graves' disease. One can, however, say that there are certain glands which show changes so characteristic that Graves' disease can be diagnosed from the microscopic appearances.

The gland in Case 1 was obtained at a time when iodine therapy was not given as a preliminary to operation. In those days the thyroid gland in Graves' disease rarely contained any considerable amount of definite colloid. Characteristically it contained little or no colloid. It is unnecessary to describe the other characteristic features, because in seeking an illustration of the acolloid goitre in Graves' disease of those days it would be difficult to find an example more typical than the gland in Case 1.

Cases 2 to 5 were obtained in the period during which iodine therapy has been in vogue. In this period the glands in Graves' disease have shown variable, but considerable, quantities of colloid. The characteristic changes may be summarized as follows (Plate 23, Fig. 12). There are large, often very large, acini and small acini. Most of the large acini contain colloid

A variable, but conspicuous, number have a sinuous outline. The degree of sinuosity varies in the same case or in different cases. The most sinuous acini resemble dilated branched tubules, forks from branches causing a resemblance to stags' antlers. From this picture there are transitions, through vesicles with papillary projections between deep bays, to vesicles with crenated margins. Even when large round vesicles with smooth margins are present they are rarely lined with flattened homogeneous cells. The lining of almost all colloid vesicles consists of larger cubical or columnar cells, which show fine or coarse vacuolation. Further, in many acini the colloid contains near the epithelial lining either clear vacuoles or eosinophil spheres. The large acini lie in a matrix of small acini, and there are transitions between the large and the small. The relative area occupied by the large and the small varies in different cases, but even when the large occupy the greater area, the small are very numerous and widely distributed. Some of the small acini are tubular, and such often show branches; others are oval or round. Some contain colloid, usually faintly stained, but very many are empty or contain only a few shreds of faintly stained coagulum. The small acini are lined with finely or coarsely vacuolated, large cubical or columnar cells. The sinuosity of the acini is evidence of an enlargement by epithelial proliferation in excess of the storage of colloid, while evidence of active secretion or transference of colloid is given by the marginal vacuoles or eosinophil spheres in the colloid, the abundance of acini containing little or no colloid, and above all the great preponderance of the large cubical and columnar epithelial cells with abundant vacuolated cytoplasm. In glands showing these characteristic signs of activity the difference between the size of individual lobules is usually inconspicuous. Very rarely is the inequality so great that the goitre is definitely nodular. In a considerable number, however, of characteristic glands, single lobules or groups of lobules may be greatly enlarged and rounded by a great proliferation of hollow or solid acini of atypical appearance, and the centres of such nodules are frequently degenerated. Such nodules suggest, and for convenience may be called, adenomata. In addition to the characteristic criteria, certain other changes are common. Desquamation of epithelium can always be found in places and it may be a conspicuous feature. There are almost always areas of lymphocytic infiltration, and such infiltration may be great. Epithelial cells with giant nuclei are frequent. There may be areas occupied by small acini in which the epithelium is so vacuolated as to recall a Grawitz tumour. There may be acini, with or without a lumen, that contain abnormally large epithelial cells with deeply eosinophil, finely granular cytoplasm; such acini are, possibly, exhausted acini.

Accepting as signs of activity sinuosity of outline of acini, marginal vacuoles or eosinophil spheres in colloid, small acini containing little or no colloid, and cubical or columnar cells with abundant vacuolated cytoplasm, Case 2 is the least active of the four glands under discussion, while Cases 5, 3 and 4 are in order of increasing activity. But in none are such signs of activity sufficient to give the picture described as characteristic of Graves' disease. Very few

of the large acini have a sinuous outline, even in Case 4. In the lining of the large acini flattened small cells with relatively little homogeneous cytoplasm predominate, while vesicles or eosinophil spheres in the colloid are exceptional. The number of small acini with little or no colloid is greater than in normal glands in all cases, being very much greater in Cases 3 and 4, but in all cases it falls short of the amount characteristic of Graves' disease. There is, in short, more evidence of colloid retention and less evidence of colloid secretion or transference than in goitres characteristic of Graves' disease. Glands in all cases of Graves' disease do not, however, show the characteristic picture described. In some sections, or in all, they may resemble closely the glands under discussion. In order to determine the relative frequency of glands similar to those in Cases 2 and 5, I examined sections of material obtained from 50 consecutive partial thyroidectomies for Graves' disease in 1932 to 1934. In all cases exophthalmos was present as well as tremor of the hands, tachycardia, and other signs of thyrotoxicosis. All patients had been given iodine before operation, usually for one to two weeks. In all save five cases two or more large slices of the goitre had been embedded in paraffin.

Of the 50 goitres 33 show the characteristics described. Adenomatous nodules are present in five. In two of the cases in which there are adenomata, the toxic symptoms were preceded for eleven and five years respectively by a history of goitre, so that the Graves' disease was secondary. In a third case the Graves' disease was primary, but it had been present with intermissions for twelve years. Among the cases in which adenomata were not found there were two examples of secondary Graves' disease.

In two glands areas of characteristic appearance are present, but the bulk of the sections is occupied by small acini, either empty or filled with colloid, which are lined with exceptionally large, often eosinophil epithelium and are separated by a diffuse lymphocytic infiltration. The histories were of primary Graves' disease.

In 10 glands the changes are transitional between the characteristic and those in Cases 2 to 5. In three of these about half of the portions of gland cut is characteristic, while half shows only a little more activity than Cases 2 to 5. One of these was an example of secondary Graves' disease. In one case the sections show all transitions from the characteristic picture to that in Case 2. This was an example of primary Graves' disease of two years' duration with an intermission, and the patient had been treated with iodine before admission to hospital. In five cases the appearances are very similar to those in Cases 2 to 5, but more activity is shown by a slightly greater proportion of small acini without colloid, less flattening of epithelial cells, and in some cases more crenation of vesicles and more vesiculation of colloid. In one of these five glands adenomata are present. All five were examples of primary Graves' disease, but in one the symptoms, including exophthalmos, had been intermittent for five years. In one case the gland is very like that of Case 2, but in one of three sections there is a small area of characteristic appearance.

In four cases the appearances resemble those in Cases 2 to 5. In three of these

the appearances are most like those in Case 3, but in only one is the lymphocytic infiltration as great. One patient had had a long treatment with iodine from her doctor. Another had secondary Graves' disease, having first had a goitre for three years and then an attack of Graves' disease six years before admission to hospital; her condition improved greatly after three weeks in bed, but recurred six months before admission. In one case the gland is most like Case 4, though it is not so grossly nodular. The patient had had several courses of iodine from her doctor.

In one case the gland shows evidence of more colloid storage and less active secretion or transference than in Cases 2 to 5. The goitre was nodular. This was a case of secondary Graves' disease, the patient having had a goitre for nineteen years before toxic symptoms and exophthalmos gradually appeared. She had had four 'adenomata' removed at an operation eight years before the onset of Graves' disease.

In 50 consecutive cases of Graves' disease, therefore, in which iodine had been given before operation, the microscopic appearances of the thyroid glands were characteristic in 33; were transitional between the characteristic and those in Cases 2 to 5 in 10; resembled those in Cases 2 to 5 in four; and showed still less activity in one. The number of cases examined is not sufficient for accurate statistics, but it appears that the characteristic histological expressions of activity tend to be less marked or absent when the symptoms are of mild intensity or intermittent so that the illness is of relatively long duration or when long treatment with iodine has been given and tolerated. From the data examined, however, it is not possible to distinguish two different diseases by the presence or absence of the characteristic microscopic picture; it is not even possible to separate primary and secondary Graves' disease. It follows that it is not possible to say that the changes in the glands in Cases 2 to 5 are incompatible with Graves' disease. It is only possible to say that they correspond to findings that are unusual in Graves' disease and are of a kind that was found in only five out of a series of 50 glands.

*The oculomotor muscles.* In Case 1 there were perivascular lymphorrhages in the five oculomotor muscles examined, the levator palpebrae superioris and a sternohyoid muscle. The muscle fibres were unaltered. The only preparations of muscle in Graves' disease at present in the Institute are vertical sections made by Dr. Dorothy Russell through the contents of one orbit close to the optic foramen and also immediately behind the protruded globe. The inferior oblique is not included in the sections. Six examples of exophthalmic goitre were thus examined. In five there is no infiltration of the eye muscles. In one of these there had been no treatment with iodine, and the thyroid microscopically is a typical acolloid goitre of Graves' disease; in the other four the thyroid gland shows the characteristic picture of Graves' disease after treatment with iodine. In three of the five cases the thymuses were glandular and weighed 21.8, 32.4, and 64.9 gm. respectively. In the other two the thymus appeared to be completely adipose to the naked eye. In one case there are lymphorrhages in all the five oculomotor muscles

included in the sections. The thyroid gland shows very conspicuously the changes which have been described as characteristic of Graves' disease treated with iodine; the thymus was glandular and weighed 32.7 gm. In this series of six cases, therefore, lymphorrhages were found in the oculomotor muscles in only one; they were then found in all muscles examined. Unfortunately, the negative findings are not convincing because, as shown by Buzzard (1905) and Dudgeon and Urquhart (1926), extensive section of a muscle may be necessary to show a lymphorrhage.

*Case 6. C.B. Male. (Plate 21, Fig. 1.)*

*A. Haematoxylin and eosin section of thyroid gland, Charing Cross Hospital, 2982/36.* The lobules vary in size, and their normal angular pattern has become somewhat rounded. Most of the acini are much larger than normally and contain colloid. Small acini are in general relatively scanty, but they are present in all lobules and predominate in a few. The large colloid vesicles are almost always of some sub-angular shape. Some show papillary projections. They are usually lined in the whole or part of their circumference with large, finely vesicular, cubical or columnar cells. Giant nuclei are occasionally present. Large vesicles lined completely with small flattened cells are rare. The colloid often shows a zone of vacuoles close to the epithelium. Some of the small acini are colloid vesicles lined with small, flat epithelial cells. These tend to be in groups within lobules in which large colloid vesicles are relatively scanty. The other small acini are lined with finely vesicular, large cubical or columnar cells. Their lumina are empty, or contain threads of coagulum or a bubbly colloid. There are two areas of lymphocytic infiltration. The picture differs in certain respects, for instance in the lack of uniformity of the affection of the lobules, from that which is characteristic of acute Graves' disease treated with iodine. A similar picture is, however, found in some examples of Graves' disease, and I should expect this gland to have been associated with definite signs of thyrotoxicosis.

*B. Tissue removed from orbit by Professor Cairns, S.D. 271/36.*

The tissue was fixed in 4 per cent. saline formaldehyde and embedded in paraffin. Sections were stained with haematoxylin and eosin, Weigert's iron-haematoxylin and van Gieson, Mallory's phosphotungstic-acid haematoxylin, Weigert's fuchselin and neutral red, and by the method of Loyez.

(1) *Two fragments of periorbita.* There is a considerable amount of recent haemorrhage. The venules contain numerous neutrophil leucocytes, and many are surrounded with a zone of infiltration with leucocytes. There are many areas occupied by a conglomerate of greatly distorted, structureless, threadlike nuclei. The changes are recent and are of a kind frequently seen in tissue removed at operations upon the brain. They are undoubtedly caused by manipulation during the necessarily protracted operative procedure.

(2) *Fragments of bone from orbit.* The fragments consist of lamellar bone forming a narrow cortex and a diploe of wide medullary spaces, in which adipose cells preponderate over haematogenous cells. There is recent, doubtless operative, haemorrhage into the diploe in many places.

(3) *Portion of levator palpebrae superioris.* The preparations were compared with similarly prepared sections of the same muscle taken at necropsy from a man, aged 40, who died from heart failure, cardiovascular hypertrophy, and nephritis repens. The most conspicuous differences in the specimen when compared with the control are recent haemorrhages accompanied by serous exudate, rarefaction of the interstitial tissue, apparently from oedema, and great enlargement of muscle fibres. The diameters of 100 muscle fibres were measured in the specimen and in the control. In the control the minimal and maximal diameters were 7 and 24  $\mu$ , the mean 14.6  $\mu$  and the mode 15  $\mu$ . In the specimen the minimal and maximal diameters were 15 and 60  $\mu$ , the mean 30.8  $\mu$  and the mode 25  $\mu$ . The muscle fibres in the specimen show longitudinal and cross striation, but the cross striation is less distinct than in the control. In sections cut at the same thickness and stained synchronously most of the fibres in the specimen are stained less deeply than in the control, but some large fibres are stained as deeply. All other changes that are seen in the specimen, such as crenation of muscle fibres and separation of their fibrils by longitudinal clefts, are present also in the control. The areas that are not haemorrhagic are not engorged. The preparations are not suitable for the detection of changes in the nerves. The haemorrhages and serous exudate are doubtless due to the operative removal. The specimen does not, however, show the signs of protracted removal that were found in the periorbita. It is unlikely, therefore, that the general oedema, and most unlikely that the enlargement of the muscle fibres, is the result of operative interference. The nature of the change in the muscle fibres is obscure. The diminution in distinction of cross striation and in depth of staining is against pure hypertrophy and in favour of degeneration or possibly oedema. The pallor is not, however, constant. It is not possible to decide whether there was engorgement before removal in a specimen in which haemorrhages have been caused by operative interference. The appearances in the present specimen do not suggest engorgement before removal.

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FIG. 1, Case 1. Exophthalmic ophthalmoplegia developing after subtotal thyroidectomy: bilateral exophthalmos with paresis of ocular movements of both eyes in all directions and bilateral papilloedema. (Case 6 in pathological report)



FIG. 2, Case 1. Left inferior rectus; perivascular lymphorrhage. Haematoxylin and eosin. (Case 6 in pathological report)

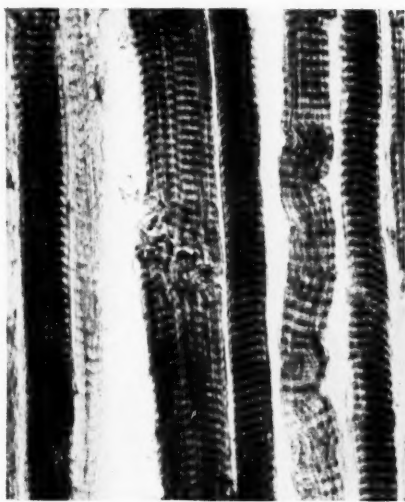


FIG. 3, Case 1. Left inferior rectus. Mallory's phosphotungstic-acid haematoxylin. (Case 6 in pathological report)



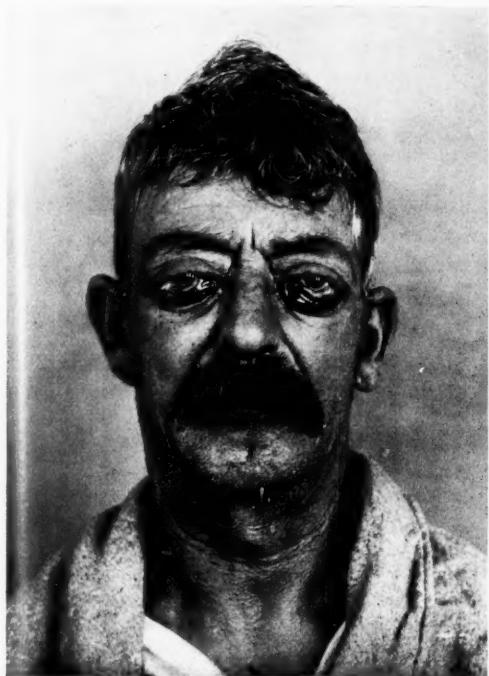


FIG. 4. Exophthalmic ophthalmoplegia with severe oedema of the conjunctivae and marginal ulceration of the corneae

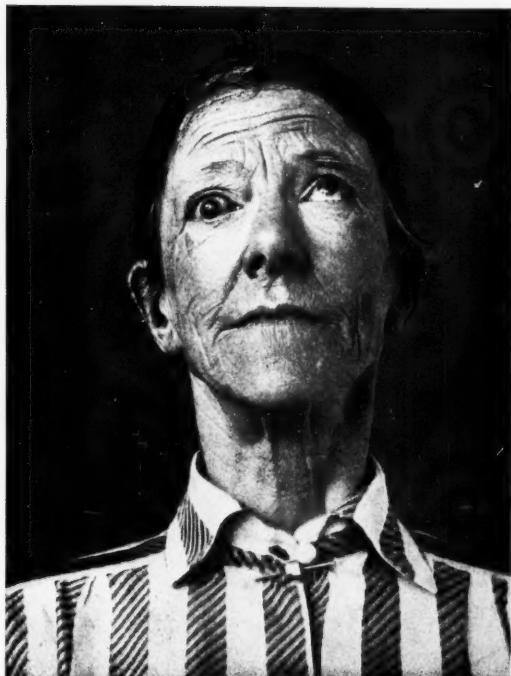


FIG. 5. Exophthalmic ophthalmoplegia: exophthalmos and paralysis of elevation, limited to the right eye. Case 4

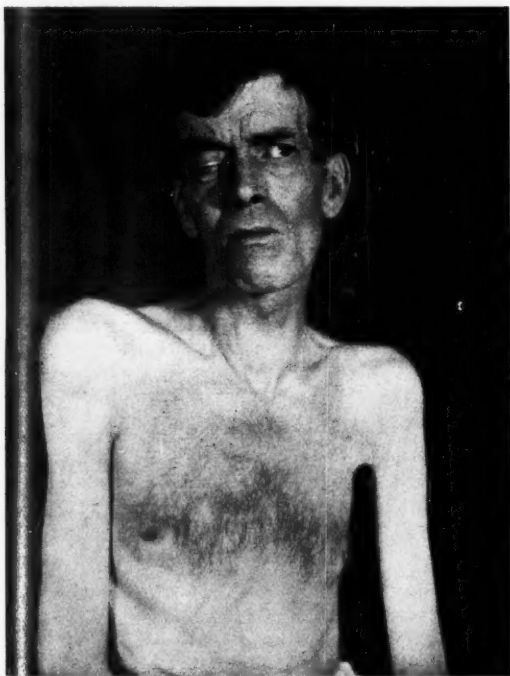


FIG. 6. Exophthalmic ophthalmoplegia associated with chronic thyrotoxic myopathy. Case 5

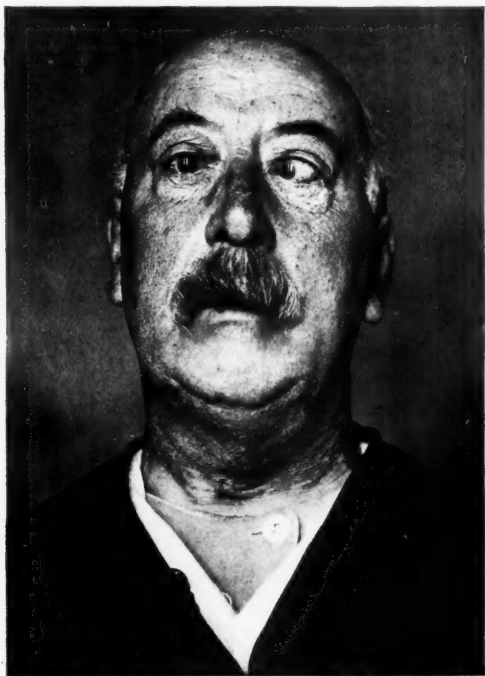


FIG. 7. Exophthalmic ophthalmoplegia twenty years after the onset of the illness. Note the pigmentation of the face and neck



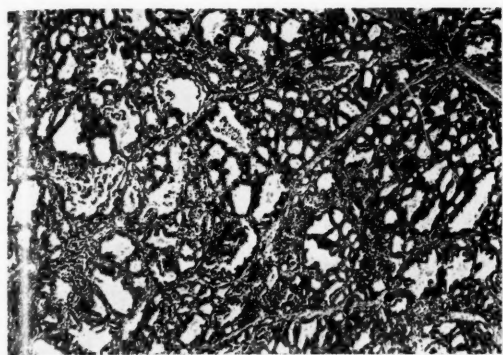


FIG. 8, Case 1. Right lobe of thyroid. Haematoxylin and eosin

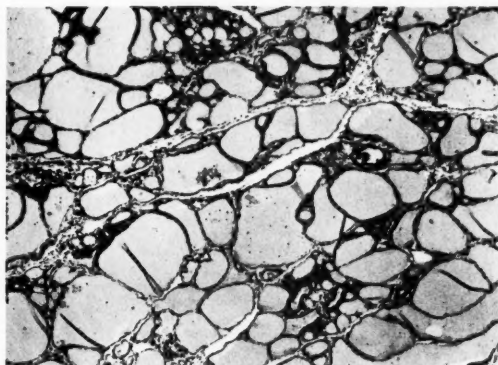


FIG. 9, Case 2. Right lobe of thyroid. Haematoxylin and eosin

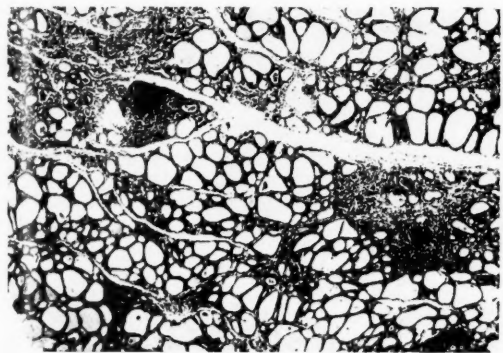


FIG. 10, Case 3. Right lobe of thyroid. Haematoxylin and eosin

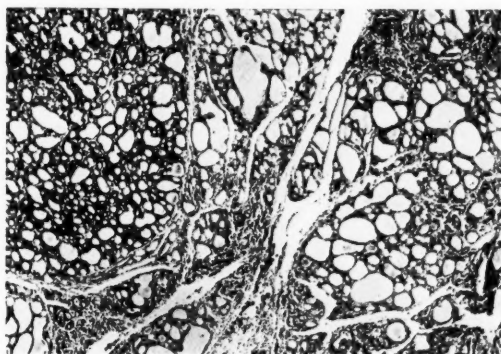


FIG. 11, Case 4. Thyroid. Haematoxylin and eosin

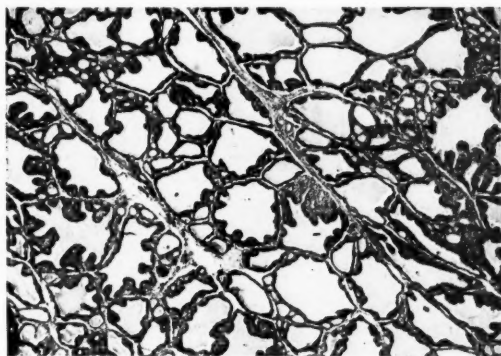
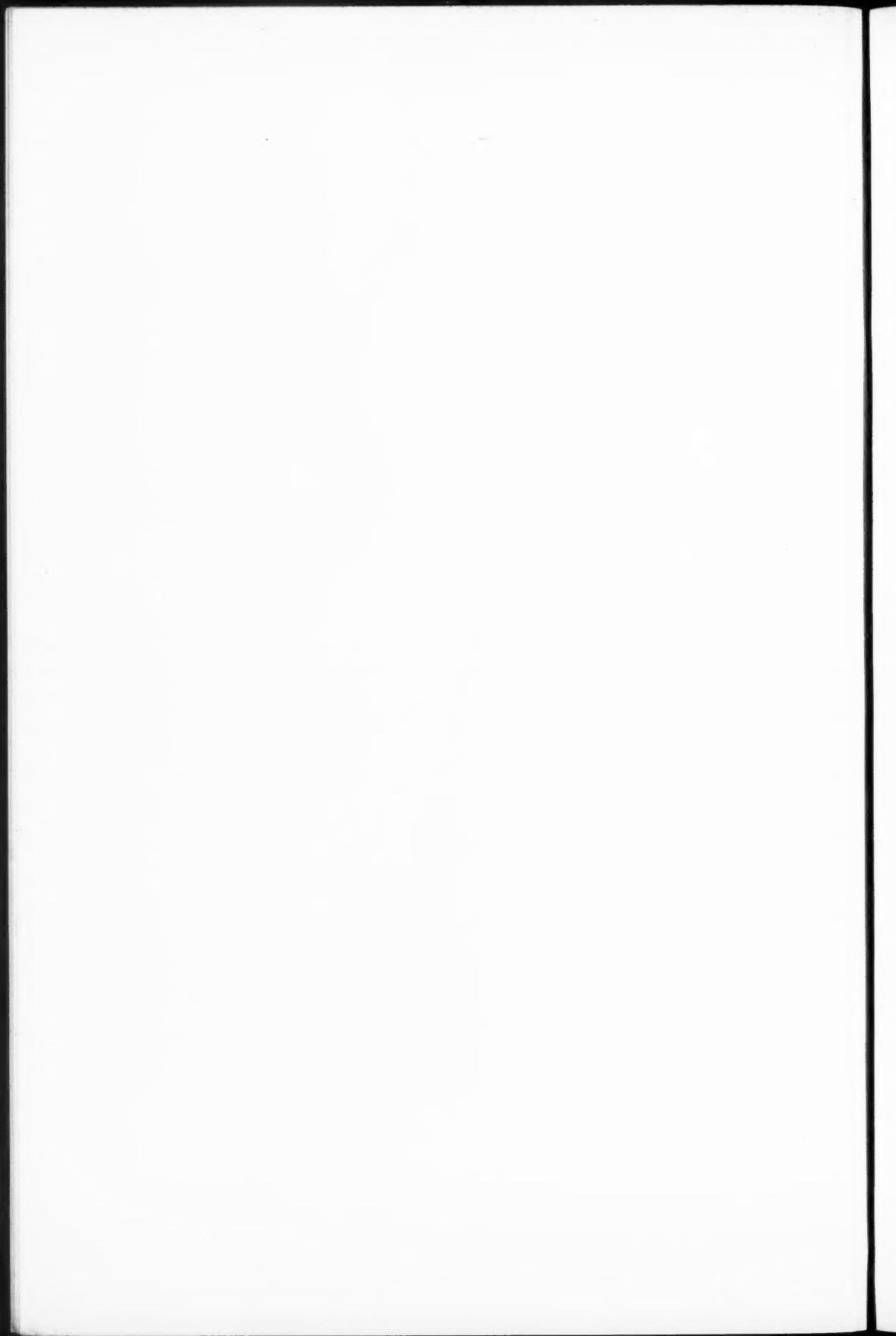


FIG. 12. Thyroid of primary Graves' disease; history of seven months' illness; iodine therapy for 10 days. Haematoxylin and eosin



FAMILIAL IDIOPATHIC METHAEMOGLOBINAEMIA<sup>1</sup>

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THE purpose of this report is to describe the findings in two cases of *familial* idiopathic methaemoglobinaemia. As far as could be ascertained from the literature, these are the first two cases in which the diagnosis was definitely established. In the case of idiopathic methaemoglobinaemia described by Hitzenberger (1932), two brothers also apparently had had cyanosis since birth, but they were not available for investigation.

*Case Reports*

*Case 1.* A French Canadian man, aged 37 years, was admitted to the Montreal General Hospital on January 18, 1937. The chief complaints were (a) bluish discoloration of the skin, most noticeable in the lips, (b) constipation, and (c) periodic attacks of abdominal pain and vomiting. Past history: he was born and had spent his whole life in the Province of Quebec. He had no recollection of having had any of the common diseases of childhood and was apparently well until the age of 11 or 12 years when he first noted the bluish discoloration of his skin. The colour varied slightly in intensity at times, but never disappeared completely. As far as he could recollect, he had never been exposed to any of the poisons which are known to cause cyanosis. Except for the cyanosis, occasional slight headaches and three or four common colds a year, he was apparently perfectly well until February 1932, when he was operated upon for a previously symptomless duodenal ulcer which had suddenly perforated. The cyanosis of the skin and mucous membranes was noted at the time of the operation and also during the entire time he was in the hospital. The anaesthetist made the observation that the cyanosis was not influenced by administration of oxygen. Apart from the surgical lesion, the physical findings were then negative, except for some pleural thickening at the base of the right lung, slight enlargement of the heart to the right, and a 'temporary rough diastolic apical murmur'. The cyanosis was, therefore, then attributed to some congenital lesion of the heart. The blood had not been examined spectroscopically. After he was discharged from the hospital he attended the Medical Out-door Clinic periodically because of constipation and occasional attacks of epigastric pain and vomiting. The cyanosis was frequently recorded during these visits and at no time was there a history of any medication with drugs known to cause cyanosis.

*Physical examination:* Except for the cyanosis and for tenderness over the whole left side of the abdomen, the clinical findings were essentially negative.

<sup>1</sup> Received January 29, 1938.

*Laboratory data:* Urine: colour, normal. Albumin, absent. Blood, absent. Sugar, absent. Urobilinogen, present 1 in 50 dilution (Wallace and Diamond method). Microscopic examination, occasional pus cell in centrifuged sediment.

Blood: Red cells, 5,260,000 per cu. mm. White cells, 8,200 per cu. mm. Wassermann, negative. Urea nitrogen, 14 mg. per 100 c.c. Creatinine, 1.42 mg. per 100 c.c. Sugar 0.117 mg. per 100 c.c. Chlorides (as plasma NaCl) 0.560 mg. per 100 c.c. Bilirubin, 1.0 unit (0.4 mg. per 100 c.c.).

Fractional gastric test-meal: Maximum total acidity, 94 c.c. N/10 acid. Maximum free hydrochloric acid, 78 c.c. N/10 acid. Faecal matter, none (sought for as evidence of a gastro-colic fistula).

Faeces: Consistency, very hard. Colour, light brown. Reaction, alkaline.

X-rays: (a) Barium meal. Evidence of old gastro-enterostomy with closed pylorus; no evidence of gastro-colic fistula. (b) Barium enema. Fistula between the distal portion of the transverse colon and the greater curvature of the stomach. This suggested that the gastro-colic fistula functioned only under pressure from the colon during a barium enema.

*Progress:* There was no vomiting or abdominal pain at any time while he was in the hospital. Operation was, however, advised in view of the past history and X-ray findings, but was refused.

*Investigation of the cyanosis.* The striking feature was the bluish-grey colour of the skin and mucous membranes, with no respiratory distress and no improvement on administration of oxygen. The heart and lungs were apparently normal according to the physical findings, X-ray examination, and the electrocardiograph. There was no clubbing of the fingers or toes. A history then obtained, of additional interest, was the fact that a sister, aged 43 years, had also had cyanosis since she was 11 years old, but was in good health otherwise. To the patient's knowledge, no other members of the family had shown cyanosis. In view of the cyanosis, which could not be accounted for by disease of the heart or lungs, it was considered advisable to make a more thorough examination of the blood with respect to the possible presence of abnormal pigments. The following were the findings: The blood when withdrawn was unusually dark in colour and remained so even after exposure to air, but it had no definitely brownish tint. No abnormal pigments were, however, found in the first spectroscopic examination made on February 2, 1937. Dr. H. N. Segall, who saw the case in consultation, suggested repeated spectroscopic examinations, because the clinical picture still suggested that the cyanosis was due to some abnormal compound of haemoglobin. The blood was therefore again examined on February 11, 1937, and methaemoglobin was found. It was also found at all subsequent examinations and was present in the red cells only; none was found in the plasma and urine. The pigment was identified and estimated. Qualitative tests: (a) An absorption band at the 6330 Å position of the spectrum.<sup>2</sup> (b) Immediate disappearance of the band by treatment of separate samples of laked blood with a drop of each of the following aqueous solutions—potassium cyanide, ammonium sulphide, and Stokes' reagent. Quantitative tests: The amount of methaemoglobin was estimated quantitatively by determining the difference between the total haemoglobin by Wu's cyanhaemoglobin method (1923) and the oxygen carrying haemoglobin by Van Slyke's method (1918, 1921).

<sup>2</sup> The authors wish to thank Dr. K. A. Evelyn, of McGill University, who determined the exact position of the band.

Total haemoglobin	= 16.0 gm. per 100 c.c. of blood.
Haemoglobin capable of carrying oxygen	= 14.6 " " "
Methaemoglobin	= 1.4 " " "

According to Lundsgaard and Van Slyke (1923) cyanosis generally occurs when the amount of reduced haemoglobin of capillary blood is greater than 5 gm. per 100 c.c. It was therefore considered of interest to determine whether methaemoglobin behaves in a similar manner. The following data were obtained under strictly basal metabolic conditions:

Total haemoglobin	= 15.6 gm. per 100 c.c. of blood.
Oxygen capacity	= 18.8 vols. per cent.
Arterial oxygen content	= 16.5 " " "
Venous oxygen content	= 14.2 " " "

From these data the following values were calculated:

- (a) Haemoglobin capable of carrying oxygen = 14.0 gm. per 100 c.c. of blood.
- (b) Methaemoglobin = 1.6 " " "
- (c) Reduced haemoglobin of arterial blood = 1.7 " " "
- (d) Reduced haemoglobin of venous blood = 3.4 " " "
- (e) Reduced haemoglobin of capillary blood  $\left(\frac{c+d}{2}\right)$  = 2.6 " " "
- (f) Reduced haemoglobin plus methaemoglobin of capillary blood (b + e) = 4.2 " " "

It is of interest to note that a moderate, but very definite, cyanosis was present when the total amount of haemoglobin which was not carrying labile oxygen was 4.2 gm. only. These data are in accord with the observation by Peters and Van Slyke (1931) that cyanosis due to methaemoglobinaemia appears to be more intense than that caused by a similar concentration of reduced haemoglobin.

*Nitrite contents of blood, urine, and saliva.* In order to ascertain the cause of the methaemoglobinaemia it was necessary to consider the possibility of an 'enterogenous' cyanosis due to nitrites. The blood was therefore tested for nitrites by the method described by van den Bergh and Grutterink (1906) and the urine by the method previously described by one of the authors, Bensley (1936). The saliva was examined by direct addition of the Griess-Ilosva reagent to serial dilutions of the material with water, and comparison of the colours obtained with those given by an aqueous solution of sodium nitrite of known strength. No nitrite was detected in the blood. The urinary concentrations of nitrite were high at the first examinations (1 in 1,500,000 to 1 in 4,000,000), but the later values were within the normal limits (1 in 15,000,000 to 1 in 40,000,000). A fact of diagnostic importance was that the reduction of the nitrite content of urine to the normal range of variation was not accompanied by any change in the intensity of the cyanosis, nor in the amount of the methaemoglobin in the blood. The nitrite content of the saliva was normal; the values were similar to those obtained in control subjects, namely, 1 part in 200,000 to 1 in 700,000.

*Bacteriology.* Urine, saliva, and faeces were examined for the 'nitrosobacillus' by the methods described by Wallis (1913) and Garrod (1925). The findings were negative.

*Drugs.* During the seven weeks while the patient was in hospital, and was never free from cyanosis, special precautions were taken to exclude any drugs which are known to cause cyanosis.

*Case 2.* E.C., French Canadian woman, aged 43 years, sister of the patient described as Case 1, was investigated because of her brother's statement that she also had the same discoloration of the skin. The examination, however, was not as complete as in the first case, since she was available for one day only. Her history was as follows: The cyanosis was first noted when she was 11 years old, and though it has never disappeared entirely since then, it has varied in intensity. Apart from the cyanosis and constipation, she has always been well. There was also no history of any medication at any time, nor of exposure to poisons which are known to cause cyanosis. She is married and has eight children, none of whom have ever had cyanosis, and, except for her brother, she knows of no other cases in the family. Physical examination was entirely negative except for the cyanosis. There was no clubbing of the fingers or toes. The urine was normal in colour and free from albumin, blood pigments, and glucose. The centrifuged sediment contained five pus cells per high-power field. The blood was slightly dark in colour when withdrawn and remained so even after exposure to air. It contained 4,450,000 red cells and 6,350 white cells per cu. mm. As in the first case, methaemoglobin was found in the red cells only; there was none in the plasma or urine. The quantitative findings were as follows:

Total haemoglobin	= 14.4 gm. per 100 c.c. of blood.
Haemoglobin capable of carrying oxygen	= 13.7 " " "
Methaemoglobin	= 0.7 " " "

The nitrite contents of the urine and saliva were normal. The blood was not tested for nitrite. No 'nitroso-bacilli' were found in the urine or saliva. The faeces were not examined.

#### Discussion

According to the literature there are four different types of methaemoglobinaemia, (a) that due to poisons (drugs, &c.), (b) that associated with certain haemolytic processes, (c) enterogenous methaemoglobinaemia, due apparently to gastro-intestinal disturbances, and (d) idiopathic methaemoglobinaemia, probably due to some 'inborn error of metabolism.'

*Poisons:* The commonest cause of methaemoglobinaemia is one of these. The poisons include acetanilide, antipyrine, phenacetin, &c. This form of methaemoglobinaemia is excluded in the two cases reported here, since, as stated, there was no history of exposure at any time to any of these compounds. Furthermore, in Case 1 drugs were definitely excluded while the patient was in hospital. It should be noted that methaemoglobinaemia due to poisons generally disappears within twenty-four to seventy-two hours after the drug has been discontinued (Eusterman and Keith, 1929; Harrop and Waterfield, 1930; Paton and Eaton, 1937; Bensley and Ross, 1937).

*Haemolytic processes:* These conditions include infection by anaerobic bacteria, eclampsia, paroxysmal haemoglobinuria, haemolytic icterus, black-water fever, &c. (van Lier, 1933). In the cases reported here, these are

obviously excluded by the history and physical examination. It should also be noted that in methaemoglobinaemia due to haemolysis the pigment is present in the plasma, whereas in the cases reported here it was confined to the red blood-cells.

*Enterogenous cyanosis.* This form of methaemoglobinaemia appears to be due, in some cases at least, to excess production and undue absorption of nitrites from the gastro-intestinal tract (van den Bergh and Grutterink, 1906; Lichtenbelt, 1923). In other cases (Lichtenbelt, 1923; van den Bergh, 1905; Lloyd, 1924; Waterfield, 1928; Miller, 1930; Leiner and Minibeck, 1935; Henstell and Dameshek, 1936) the diagnosis of enterogenous cyanosis was suggested from the history and physical examination, but there were no examinations for nitrites in some, and in others the data were inconclusive. In the two cases reported here, enterogenous cyanosis is excluded by the clinical history and the failure to detect any undue absorption of nitrites from the intestinal tract. It should be noted that, although there was a perforated duodenal ulcer and a gastro-colic fistula in the first case, the cyanosis had antedated the symptoms for some twenty years. In the second patient mild constipation was the only gastro-intestinal abnormality.

*Idiopathic methaemoglobinaemia.* As far as could be ascertained from the literature, five idiopathic cases only have been reported previously (Hitzenberger, 1932; van Lier, 1933; Dieckmann, 1932; van Thienen, 1933; Litarczek, Aubert, Cosmulesco, Comanesc, and Litarczek, 1930). In four, the cyanosis apparently dated from birth and in the remaining case it was first noted at the age of 19 years. In all of these cases the cyanosis was constant and was not affected by any form of treatment.

#### *Summary.*

1. Two cases of familial idiopathic methaemoglobinaemia are reported.
2. The differential diagnosis of the different forms of methaemoglobinaemia is briefly discussed.
3. As far as could be ascertained from the literature, only five cases of idiopathic methaemoglobinaemia have ever been reported previously. In one of these there was a suggestive familial history, but the diagnosis of familial methaemoglobinaemia was not proven.

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THE OUTPUT OF THE HEART IN CONGESTIVE FAILURE<sup>1</sup>

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*Introduction*

THE majority of attempts which have hitherto been made to determine the cardiac output in heart failure have either been done on a number of cases too small to yield results of much value, or methods have been employed with too large a margin of error to allow much significance to be attached to the results. All attempts have been summarized by Harrison (1935) whose conclusions from the published work of others is that, on the average, the resting cardiac output seems to be lowered in heart failure. Observations of this sort do not carry us much further than the reasonable assumption already made by clinicians that, as the heart fails, its output will tend to go down. The acetylene method of determining cardiac output seems, by its relative simplicity and apparent accuracy, to offer a method of obtaining a very close approximation to the true output of the heart. Figures obtained by this method have shown remarkable agreement with the figures obtained by direct cardiac puncture in man. Baumann (1930) obtained data by the latter method from ten subjects in whom the circulation was considered to be normal; when tabulated alongside data obtained by the acetylene technique there is a close statistical agreement in the distribution of the figures (Table II). It has also been shown that estimations of the normally occurring postural change in cardiac output made by the acetylene method agree well with measurements of the degree of postural change made by a simpler and more direct method depending on changes in the rate of oxygen uptake (McMichael, 1937). The value of the method as a measure of the absolute output at rest thus seems to be reasonably established. Applied to patients with heart failure, the acetylene method has given somewhat disconcerting results. Kroetz (1930) found diminution of the cardiac output in 'compensated' heart disease, but the output did not diminish much as congestive failure appeared. Harrison (1935) found that, while the resting cardiac output was, in general, reduced in heart failure, the degree of diminution in output bore no definite relation to the degree of failure, and that clinical improvement might be accompanied by a fall in the output of the heart. By the use of a dye method of estimating cardiac output, Hamilton, Moore, Kinsman, and Spurling (1932) also found little correlation between cardiac output and the degree of heart

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failure. It stands to reason that, if these apparently puzzling results are correct, a considerable re-orientation of our views on the behaviour of the heart in cardiac failure will be necessary. A common clinical conception is that the resting output of the heart is maintained until the later stages of failure, when the output falls; in the last stage the blood gradually accumulates on the venous side of the circulation, and a rise in venous pressure occurs as a result of the inability of the heart to pass the blood on into the arteries. This conception of heart failure assumes the existence of a certain basal resting output, for which there is no real evidence. A mass of data—Field and Bock (1925), Turner (1927), Donal, Gamble, and Shaw (1934), McMichael (1937)—has now accumulated to show that even at rest the output of the heart varies considerably with the posture of the subject, the lowest output of the heart being reached at a basal rate of oxygen consumption and in the erect position. These conditions may be achieved with the subject at rest on a tilting table. When the supine position is adopted, without any change in the metabolic rate, the output increases by some 30 per cent. In this paper particular attention has been paid to the measurement of the heart output in both the erect and the reclining or supine positions in cardiac patients, and the response of the diseased heart to change of posture is compared with that of the normal. The data obtained are capable of a physiological interpretation which clarifies the apparent anomalies of the behaviour of the heart observed by Harrison and by Kroetz.

*Classification of cases.* Little value can be attached to those cardiac output measurements made in the past where attention was focused on the anatomical type of cardiac lesion, rather than on the degree of disability experienced by the patient. The crucial clinical test of cardiac function is the patient's capacity for effort of varying grades, and it is of prime importance that measurements of heart output should be correlated with the severity of the patient's symptoms judged in this manner. For this reason the cases studied have been classified functionally according to the suggestions made by the American Heart Association (1928). Group I includes cases of organic heart disease able to carry on ordinary physical activity without discomfort. Group II consists of those unable to carry on ordinary physical activity without discomfort, (a) those with symptoms brought on by moderate or considerable exertion such as climbing stairs, (b) those with breathlessness on ordinary exertion such as walking on the level. In Group III are those with marked signs of failure even at rest, who are confined to bed, and are unable to undertake any form of physical activity. The classification of a case as Group I or III is easy. The two subdivisions of Group II are more difficult to classify and are admittedly dependent on a subjective assessment of the severity of the symptoms both by the patient and the observer. It is admitted that one or two border-line cases in Group II might have been grouped 'a' or 'b' by different observers. The point is immaterial, for what is really significant in this study is that all patients in Group II b were more breathless on exertion than patients in Group II a.

I. *The Postural Changes in Heart Output and Heart-rate*

By measuring the *immediate* increase in the rate of oxygen consumption which takes place when the resting subject is quickly changed from the erect to the supine position on a tilting table, a simple measurement may be made of the percentage increase which takes place in circulating minute volume under these conditions (McMichael, 1937). By taking pulse-rates into account

TABLE I  
*Postural Changes in Minute and Stroke Volume*

	Case.	Erect.		Supine.		Percentage change in Minute volume.      Stroke volume.	
		Pulse.	Rate of O <sub>2</sub> cons. c.c. per min.	Pulse.	Rate of O <sub>2</sub> cons. c.c. per min.		
Group I.	1	45	225	41	273	+22	+32
	2	112	391	88	534	+37	+74
	3	105	391	96	550	+41	+54
Group IIa.	1	108	314	100	357	+13	+22
	2	94	360	88	402	+12	+19
	3	102	291	89	324	+14	+27
	4	—	298	—	348	+16	—
	5	—	280	—	312	+12	—
Group IIb.	1	83	269	76	272	+1	+7
	2	94	240	93	268	+11	+13
	3	96	225	86	221	-2	+10
	4	78	234	86	242	+3	-6
Group III.	1	105	161	104	148	-8	-7

the change in stroke volume may also be determined. The results obtained in a series of cardiac patients are shown in Table I and Fig. 1. As compared with a series of normal subjects it is seen that in Group I the response of the heart is within normal limits. In Group IIa it is diminished, while in Groups IIb and III no very significant response is detectable. It is also noteworthy that the great increase in stroke volume occurring in normal subjects in the supine position also disappears with the advance of cardiac disease.

*The significance of the disappearance of the postural response.* There are many reasons for believing that the increase in heart output on adopting the supine position is due to an increase in the venous pressure near the right auricle (McMichael, 1937). This pressure will be referred to subsequently as the *effective venous pressure*. The absence of postural change in cardiac output from Group IIb onwards might be due to (1) absence of any effective venous pressure change in cardiac disease, (2) inability of oxygen to diffuse sufficiently rapidly through the alveolar walls to allow of an increased rate in the oxygen uptake, or (3) inability of the heart to respond to a rise of venous pressure. These possibilities will be discussed.

1. In Group IIb the venous pressure is usually raised 2 to 4 cm. above the normal level (see Fig. 4) and it is just possible that in the presence of distension

of the veins the postural change of effective venous pressure is absent or is less pronounced. It seems unlikely that this is the explanation for the following reasons :

(a) The postural response begins to diminish in Group II *a* before any rise in venous pressure has occurred. (See also Fig. 4.)

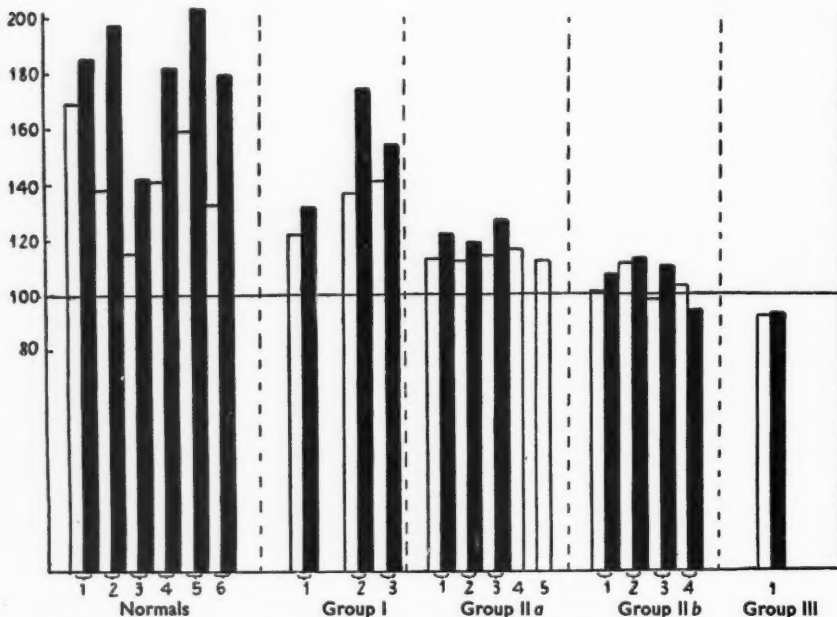


FIG. 1. Postural percentage changes in cardiac output at various grades of failure. Transverse line at 100 = 'erect' minute and stroke volume.

Open rectangle = 'supine' minute volume.

Black rectangle = 'supine' stroke volume.

The six normal subjects are taken from data of McMichael (1937).

(b) In one case of aortic incompetence (Case II *b*, 1) where there was no rise of venous pressure, the postural response was absent. Over-distension of the systemic veins was absent in this patient.

(c) The systemic venous pressure may be raised in emphysema on account of changes in intrathoracic pressure (Kountz and Alexander, 1934). Measurements of the postural response have been made in a case of emphysema in which the venous pressure was raised to 5 cm. above the sternal angle. The postural response was present and normal in degree, the cardiac output increasing by 25 per cent. in the supine position. Thus with an equivalent or even greater amount of venous distension than in Group II *b*, the postural response of the heart was still present. We may conclude, therefore, that this degree of venous distension does not abolish the change in effective venous pressure which occurs with change in posture.

2. The second possibility, viz. the inability of oxygen to diffuse sufficiently rapidly through the lung tissues, is improbable for the following reasons :

(a) Lowering of the oxygen content of the arterial blood does not occur in heart failure until pulmonary oedema is present (Fraser, 1927; Calhoun, Cullen, Harrison, Wilkins, and Tims, 1931). The disappearance of the postural response bore no relation to the occurrence of such oedema.

(b) Up to Group II *b* measurements have been made during exercise, showing that the rate of oxygen uptake can increase to 600 c.c. per minute and more (Table III). This is well above the rates of increased oxygen uptake occurring with change of posture at rest. The lungs therefore present no significant obstacle to the diffusion of oxygen at resting rates of oxygen consumption.

The most probable explanation therefore of the disappearance of the postural changes is inability of the heart to respond to the postural rise of venous pressure. As will be shown later, this explanation is supported by absolute cardiac output determinations made by the acetylene method. Such an explanation is in accordance with a reasonable physiological conception of the trend of events in cardiac failure. Starling (1918) showed that the output of the heart in unit time is directly dependent on the pressure in the great veins near the right auricle. In cardiac failure one must assume that the output of the heart cannot be increased sufficiently to deal with the increased oxygen requirements of physical exertion. The inability of the heart to make this physiological response to effort is obviously correlated (Fig. 1) with its inability to respond to the postural rise in venous pressure. The existence of this correlation is clearly against the view of Harrison (1935) who minimizes the importance of the inability of the diseased heart to increase its output. In laboratory experiments in which animal hearts were poisoned by narcotics Socin (1915) was able to show diminished ability of the heart to respond to a rise in venous pressure. Wiggers and Katz (1922) also showed that there was a distinct physiological limit to the cardiac response to venous pressure changes; when the heart-muscle became overstretched any further rise in venous pressure might be accompanied by no further rise, or even by a fall, in the output of the heart.

*The Bainbridge reflex in heart failure.* In 1915 Bainbridge described a reflex increase in the heart-rate elicited by a rise in pressure in the great veins near the right auricle. The physiological importance of this reflex has been questioned as it tends to act in an opposite sense to the carotid sinus reflex; for example, in healthy subjects the increment in the effective venous pressure produced by changing from the erect to the supine position is accompanied by a fall in pulse-rate in spite of a considerable increase in the output of the heart. It thus appears that during postural changes the carotid sinus takes precedence over the Bainbridge reflex. As cardiac failure progresses, the fall in pulse-rate accompanying the adoption of the supine position tends to become less, and when Group III is reached there is, on the average, little change of heart-rate with change of posture. The normal postural pulse-slowness thus tends to disappear with the progress of heart failure (Table I, Fig. 2). It is to be noted that Bainbridge used very

considerable rises in venous pressure (several cm. saline) to produce the effect of cardio-acceleration. Such a degree of change probably rarely occurs under normal physiological conditions. McDowall (1934) has shown that raising the venous pressure often reduces or abolishes the normal depressor effects from the carotid sinus in the intact animal. This veno-pressor

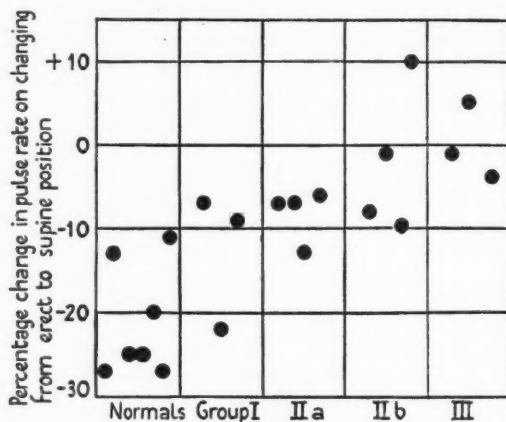


FIG. 2. The effect of cardiac failure on the postural change of pulse-rate. The normals are taken from previous observations, while the other data, with three exceptions, are taken from Table I. The normal postural slowing tends to diminish and disappear as heart failure advances.

mechanism may explain the alteration in postural pulse-rate changes occurring in cardiac patients with high venous pressures. In Case III, 1, a venesection of 500 c.c. of blood was accompanied by a fall in pulse-rate from 110 to 95 per minute, an observation which would support the idea that the high venous pressure in cardiac failure is an important factor in maintaining the high pulse-rate so frequently noted in the advanced stages.

## II. Determination of the Cardiac Output in Heart Failure.

The results so far discussed indicate only the *degree* of change in the heart output which occurs with change of posture. Determinations of the absolute cardiac output have also been made by the acetylene method. This involves determination of the arteriovenous oxygen difference in c.c. per litre of blood passing through the lungs, by rebreathing an acetylene-oxygen-nitrogen mixture. The rate of oxygen consumption is also estimated by collection of expired air in a Douglas bag and subsequent analysis. The output of the heart in litres per minute is then calculated from the Fick formula:

$$\text{Cardiac output in litres per minute} = \frac{\text{c.c. O}_2 \text{ consumed per minute}}{\text{Arteriovenous oxygen difference (c.c. per litre)}}$$

The answer is considerably influenced by the numerator of this equation. In order to get comparable results, Grollman suggested that estimations should be done under strictly basal conditions, the answers then being reduced



observations is 75 c.c. per litre with a slightly greater standard deviation. Although there is some overlapping of the polygons it must be noted that in every individual case there was an increase in the arteriovenous oxygen difference in the erect as compared with the reclining position. In my personal observations this amounted to an increase in the cardiac output in

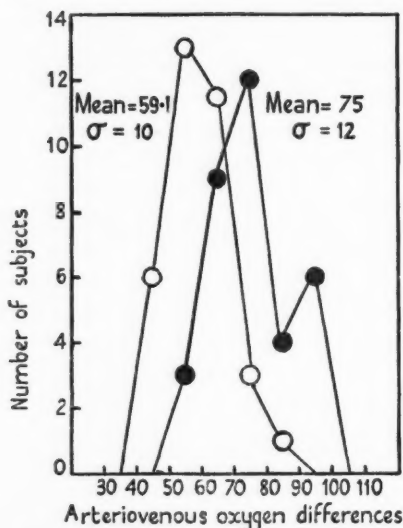


FIG. 3. The distribution of arteriovenous oxygen differences in 34 normal subjects in the erect (solid) and supine (circle) positions.

the supine position of more than 30 per cent. In the collected data in the table, however, the increase is slightly less, viz. 27 per cent. Taking our normal standards from these observations the cardiac output of normal subjects in the supine position is  $100/59$  or 1.67 litres per 100 c.c. oxygen consumed, with a standard deviation ranging from  $(100/69)$  1.45 to  $(100/49)$  2.04 litres per minute. Similarly in the erect position the cardiac output has a mean value of  $(100/75)$  1.33 litres per 100 c.c. oxygen consumed, the standard deviation ranging from  $(100/87)$  1.15 litres to  $(100/63)$  1.59 litres. These values have been ruled as lines indicating the normal ranges in Fig. 4.

*Method.* The exact method used in these determinations is that described in another paper (McMichael, 1937) involving the use of higher concentrations of acetylene than those used by Grollman and a different method of analysis. The results obtained are not accepted unless subjected to careful checks. In checking the results the following methods are adopted:

1. Double determinations are made by the three-sample technique (Grollman, Friedman, Clark, and Harrison, 1933), and results which vary by more than 7 per cent. from their mean value are discarded.
2. Successive determinations may be made at short intervals under identical conditions, and results agreeing to within 10 per cent. of one another may be accepted.

3. Where postural change in cardiac output is present, the degree of change may be confirmed by the postural oxygen consumption method used in making the observations in Part I.

4. Confirmatory evidence of considerable fluctuations in cardiac output may be afforded by the inverse relationship which has been shown to exist between the cardiac output and the ventilation equivalent (McMichael, 1937). This relationship, however, is only statistical, and it is possible for the cardiac output to change within a 20 per cent. range without much alteration in the ventilation equivalent.

By applying the method with these precautions the results can probably be relied upon to give a measure of the output of the heart within plus or minus 10 per cent. of the real value, and in intelligent co-operative subjects possibly to within 5 per cent. (e.g. Case II b, 3).

*Applicability to cardiac patients.* On the whole, the method is easier to apply in moderate degrees of cardiac failure than in normal subjects, the frequency of accurate checks by the three-sample technique being higher. The advantage probably results from (a) the lower lung volume resulting from pulmonary congestion giving a smaller total volume of gas in the lung-bag system; as a result of this the disappearance of equivalent volumes of acetylene into the blood gives larger and therefore more significant percentage differences in acetylene and oxygen concentrations in the samples, (b) the slower circulation and the increased blood-volume makes the vitiation of the samples by re-circulation of acetylene unlikely, and there is no disadvantage in prolonging the rebreathing period to 35 seconds if necessary. The one disadvantage is gross pulmonary oedema. Since acetylene is more soluble than  $\text{CO}_2$  and diffuses through the lungs more easily, a minor degree of oedema does not interfere with the diffusion of acetylene into the blood. More than a moderate amount of pulmonary oedema may lead to difficulty in achieving a uniform saturation of the lung tissues (including fluid) before the sampling is begun. Under these conditions excessive amounts of acetylene may be disappearing in oedema fluid during the sampling period. As the estimations assume that the acetylene is being removed by the circulating blood, false high results are obtained for the cardiac output. In these circumstances discordance of the checks usually occurs and shows an irregular rate of disappearance of acetylene, and the erroneous results may be discarded. Twice, however, in the course of this work (which has involved over 150 determinations of cardiac output) false high results were obtained which were wholly out of keeping with the other observations (ventilation equivalents, etc.), but which came very near to checking by the three-sample technique. Such accidental checking is very unusual, but every result must be critically examined and if it seems in any way dubious, the whole series of observations must be repeated. In the above two instances repetition of the determinations yielded more consistent results. Finally, all precautions must be taken to see that the analyses are carried out with precision and accuracy. In every case the *venous pressure* was estimated by Lewis's method (1930),

taking the upper level of visible filling in the external jugular vein and measuring from the level of the sternal angle as the base line. Measurements were made at first by the direct method of Moritz and Tabora (1910), but it was soon found that an equally accurate and satisfactory estimate could be made by Lewis's method. The venous pressure normally does not rise above

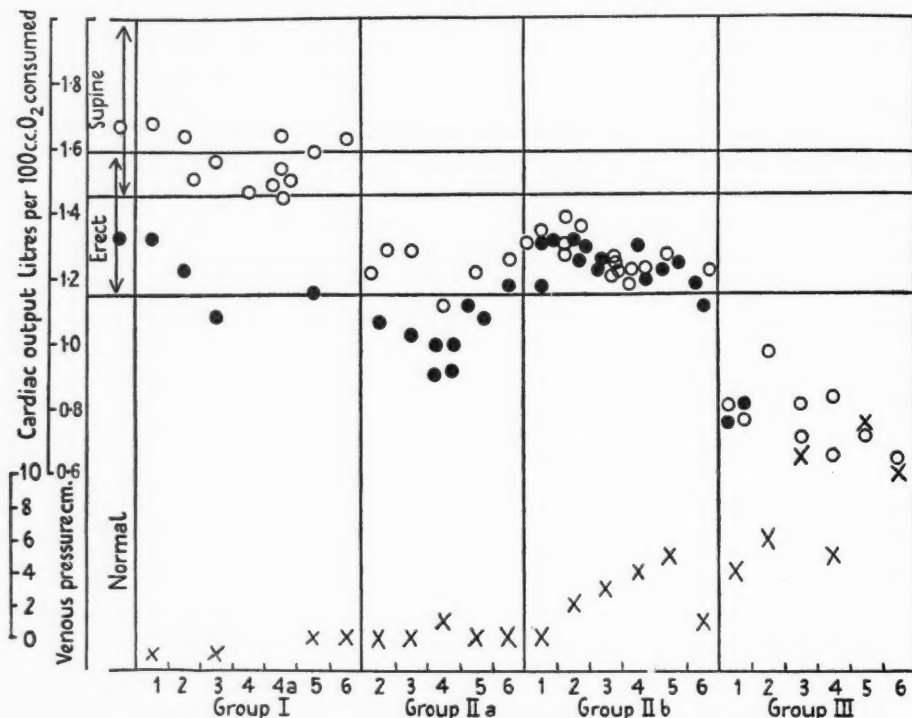


FIG. 4. Cardiac output at various stages of heart failure. Cardiac output erect (solid) and supine (circle). Each of the 71 points represents a checked determination. Transverse lines at 1.15 and 1.59 indicate the standard deviations of the normal erect output, while those at 1.45 and 2.0 give the standard deviations of the supine output. Venous pressure (crosses) in cm. above the sternal angle. Note the upward trend of output in association with the venous pressure rise in Group II b.

the level of the sternal angle. A further advantage of the latter method of taking venous pressure is that the vein used as a manometer is reasonably near the right heart. In veins farther from the heart the pressure level is influenced by alterations in peripheral flow, and may be raised or lowered somewhat by vasodilatation and vasoconstriction respectively (Doupe, Krynauw, and Snodgrass, 1938).

**Results.** The cardiac output measurements are shown in Fig. 4, classified in groups according to the clinical state of the patient. In Group I the cardiac output determinations in both the erect and reclining positions are scarcely outside the normal ranges. In Group II a the output in the erect position is on the average rather lower than normal, while in the supine

position the fall in output below the normal is still more conspicuous. The postural response of the heart is also diminishing at this stage. In Group II *b* the output in the erect and in the supine position does not change appreciably in any individual case and the outputs are remarkably constant at 1.2 to 1.3 litres per 100 c.cm. oxygen consumed in both positions. In Group III the outputs in general are falling below 1 litre and have been recorded as low as 0.6 litre per 100 c.cm. oxygen consumed. Owing to the obvious difficulty of shifting patients at this stage, only one has been subjected to the tilting table procedures. In this subject there was no significant change of cardiac output with change of posture.

*Significance of these observations.* The results obtained in this part of the investigation confirm the observations made in the previous section indicating the gradual diminution of the postural response. Further there is a diminution in the cardiac output from stage I to II *a*, and again from stage II *b* to III. There is, however, a distinct upward step between II *a* and II *b*, and this is associated with the occurrence of a rise in systemic venous pressure which makes its appearance in stage II *b*. The only exception was Case II *b*, 1, in whom, however, there was a distinct lowering of the vital capacity, possibly indicative of pulmonary venous congestion. A fall in output is very obvious at stage II *a*, but this is unassociated with any venous pressure rise. The elevation of venous pressure thus cannot be regarded as a passive phenomenon dependent on diminished cardiac output; its initial appearance is associated with a distinct rise in the cardiac output above the expected level. By Starling's law, a rise in venous pressure determines an increase in the output of the heart, and this gives good grounds for the hypothesis that the initial rise of venous pressure and the accompanying increase in cardiac output are cause and effect. It is tempting to regard the rise in venous pressure as a 'compensating' mechanism, although the exact factors concerned in its elevation still await elucidation. With the narrowing of the response of the heart to a given (postural) increase in venous pressure, the organism may possibly achieve for itself the optimum conditions by setting the venous pressure at such a level as to maintain a higher resting value of the cardiac output.

The observations here recorded indicate a certain orderly sequence of changes in the output of the heart in cardiac failure which has hitherto escaped notice. At the same time these findings do not conflict with previously recorded measurements, usually made on a much smaller series of cardiac cases, in which the output in failure has been found to be either considerably reduced or only slightly reduced below the normal level. One can also agree with Harrison that, as the clinical condition of a given patient improves, the cardiac output does not necessarily change *pari passu*. Inspection of the data in Fig. 4 shows that, with an improvement from condition II *b* to II *a* the output in the reclining positions might actually fall, although the restoration of the postural response would actually indicate an improvement in the efficiency of the myocardium.

Another question must be discussed. When the heart no longer responds

to the postural increase in venous pressure with an increase in output, does this mean that it is unable to increase its output at all? Such an effect might be expected if the diseased human heart behaved like the over-distended mammalian heart in the experiments of Wiggers and Katz (1922). They found that, once the distended heart ceases to respond to a given

TABLE III  
*Cardiac Output Measurements in a Normal and a Cardiac Subject at Various Rates of Oxygen Consumption*

Normal	Oxygen consumption in c.c. per minute.	Arteriovenous O <sub>2</sub> diff.	Cardiac output.
J. M.	240	64.5	3.72
	273	55.0	4.97
	280	63.4	4.42
	316	55.6	5.69
	331	64.5	5.13
	361	64.0	5.64
	478	60.0	7.97
Cardiac			
Group II b Case 4	208	79.5	2.64
	252	79.5	3.17
	283	81.0	3.50
	296	82.0	3.61
	482	79.0	6.09
	580	93.5	6.21

increase in venous pressure, any further rise in venous pressure does not produce an increase in the output of the heart, but may actually lead to a diminution. In discussing the methods, however, it is emphasized that we cannot expect an *exact* answer on cardiac output from the methods at present available. For this reason alone the postural effects in Group II b should not be given too much *quantitative* significance. The method is not sufficiently exact to detect with accuracy, say, a 5 per cent. change in cardiac output. There is reason to believe that the healthy heart is extremely sensitive to venous pressure changes. We know that the heart in severe exercise may increase its output six- or sevenfold, and without extreme sensitivity this could not occur without a very gross increase in venous pressure. It would not be surprising if the normal 25 to 30 per cent. increase in cardiac output were produced by a rise in effective venous pressure of 1 cm., and it is conceivable that the postural changes of venous pressure may be of this order. For this reason it is necessary to produce much greater changes than can be produced by posture to see if the failing heart does respond at all to venous pressure increments. Greater changes in venous pressure can be produced by two methods, (a) exercise, (b) a large venesection.

(a) The effects of exercise are shown in Table III and Fig. 5. All the determinations were carried out on a patient in Group II b (Case 4). He walked quietly about the ward for various distances and then immediately lay down flat on a couch, the rate of oxygen consumption and arteriovenous oxygen difference being determined forthwith. It is seen that he was able to increase his cardiac output from 2.5 to over 6 litres per minute. With an

oxygen consumption of more than 500 c.c. per minute the cardiac output does not continue to increase *pari passu* as it does in a normal subject, but may reach a plateau, the extra oxygen being supplied by an increased utilization of the oxygen-carrying capacity of the blood, that is, by an increase in the arteriovenous oxygen difference.

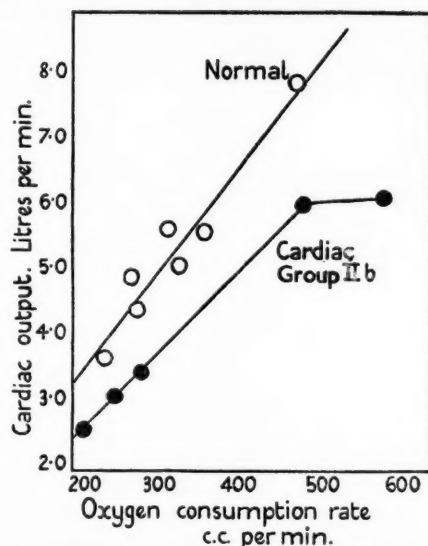


FIG. 5. Cardiac output during mild exertion in a normal (circle) and a cardiac subject (solid) at stage II b (from Table III). The output increases *pari passu* with exercise in both, but tends to reach a limit much sooner in the cardiac patient.

(b) The effect of venesection. To produce any measurable effect on the venous pressures it is necessary to do a large venesection in a subject with a very high venous pressure. It is fortunate that the latter condition is regarded as an indication for venesection as a therapeutic measure. In Case III, 5, who showed a venous pressure of 13 cm., one litre of blood was removed from an arm vein with considerable subjective relief. The venous pressure fell by 6 cm. and the cardiac output fell from 0.72 litres per 100 c.c. oxygen consumed to 0.65 litres (i.e. by about 10 per cent.). Harrison has observed similar effects in three venesections. The conclusion from these experiments is that the diminution of the postural response of the heart does not mean that the heart is unable to increase its output. It is probable that the degree of venous pressure change produced by alterations of posture is too small to produce a change in heart output measurable by the methods in use.

#### Discussion

One of the most significant features of Harrison's work on cardiac failure was the emphasis which he laid on venous congestion, and its responsibility for many of the clinical manifestations of what he called the 'dyskinetic

syndrome' of circulatory failure. He also realized the importance of raised venous pressure as a compensating mechanism. All the observations here described bear out Harrison's emphasis on the latter point. It becomes important, therefore, for us to consider the exact relation which exists between venous pressure and heart output on the normal heart. When

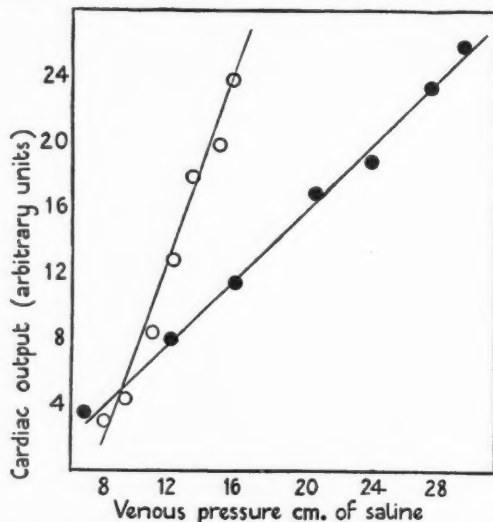


FIG. 6. The relation of venous pressure to heart output in the mammalian heart. Data are plotted from the optical records of Wiggers and Katz, experiments C 290 IV (circle), and 288 IX (solid).

Starling (1918) demonstrated that the output of the heart was essentially dependent on the venous inflow, he had to consider the mechanisms by which this effect was brought about. The possibilities were that it was produced (1) by increased lengthening of myocardial fibres without any significant change in tension, or (2) increased tension of the fibres. From his experimental observations and from certain arguments based on analogies with the behaviour of frog's skeletal muscle, Starling favoured the former mechanism. More direct observations made by Wiggers (1928) favour the latter mechanism. Wiggers and Katz (1922), using optical methods, recorded the volume changes of the ventricles and thus measured the output of the heart in response to the pressure of the venous inflow. Analysis of their data suggests that the output of the mammalian heart bears a simple mathematical relationship to the venous pressure. That this is likely is shown by plotting the ventricular volume-change of experiments described in Wiggers and Katz's paper against the venous pressures, the points falling very near a straight line. In a private communication, Prof. Wiggers has informed me that this straight line relationship seems to hold in other experimental records which he has similarly analysed. It is just possible, however, that this straight line relationship may be accidental and dependent on the recording instruments, and further information from animal experi-

ments must be awaited before finally deciding this point. Meantime, however, it is convenient and probably sufficiently near the truth to consider that in the normal heart there is a simple linear relationship between the venous pressure and the cardiac output. Wiggers and Katz (1922) showed that the over-distended heart of the dog first ceased to

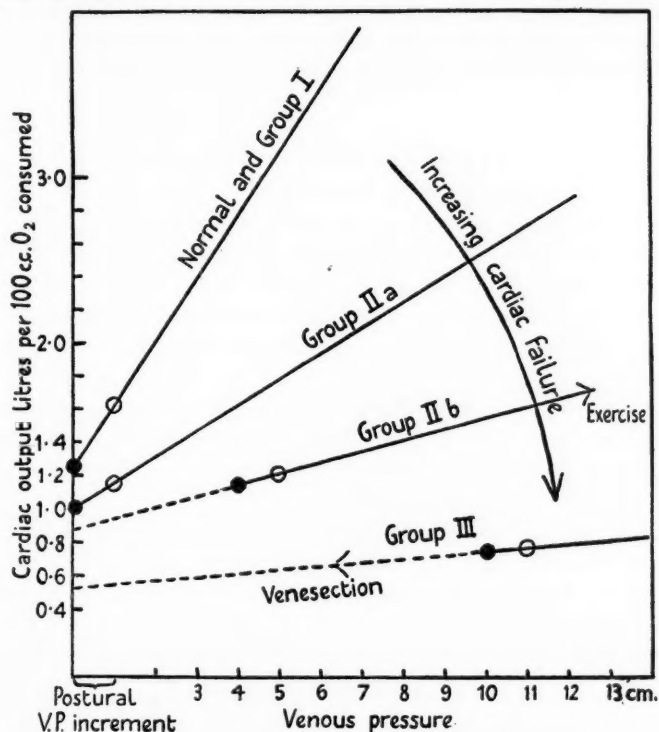


FIG. 7. Diagrammatic representation of the probable trend of behaviour of the heart in heart failure.

Erect (solid) and supine (circle) outputs are shown in relation to the venous pressure. The downward trend of output is accompanied by a diminishing response to equal venous pressure increments, and in the last two stages of the disease some 'compensation' occurs by venous pressure elevation. The points indicated by the arrows in Groups II b and III were determined by exercise and venesection respectively.

respond to venous pressure increments, and finally the output decreased with further increase of venous pressure. It is conceivable that the inability of the failing human heart to increase its output on changing posture is similar to this overload failure. The possibility is, however, unlikely, as, even in the absence of the postural response, exercise is still capable of producing an increase in output (Table III, Fig. 5). If the behaviour of the diseased heart were like that of the over-distended heart no further increase in output would be possible. Further, I have found no statistical correlation between heart size (measured radiologically by Bardeen's (1918) formula) and the degree of diminution of the postural

response. It is in accordance with the observed facts, however, to regard the diseased heart as becoming less and less sensitive to venous pressure increments. If the resting venous pressure were to remain unchanged the resting output of the heart would probably fall *pari passu* with the degree of failure. By a rise of venous pressure at Group II *b* the resting output is set at a higher level, although by the time Group III is reached even this mechanism cannot compensate appreciably for the gross diminution of cardiac efficiency. This hypothesis is set out diagrammatically in Fig. 7.

### Summary

1. By two methods it has been shown that the normal postural increase in heart output which takes place on changing from the erect to the supine position diminishes and almost disappears as cardiac failure progresses. This diminution in response of the heart to a postural increase of venous pressure is comparable to similar phenomena observed in failing animal hearts.

2. The normal postural slowing of the pulse-rate in the supine position is also lessened as failure develops. This alteration of heart-rate control is possibly dependent on a veno-pressor mechanism.

3. When the cardiac output is standardized to output per 100 c.c. of oxygen consumed, a certain regularity of behaviour of the heart becomes manifest at various stages of failure, as follows:

Group I. No significant change in output from normal values either in the erect or supine position.

Group II *a*. A distinct drop in the output of the heart in both the erect and supine positions, but especially in the latter.

Group II *b*. The output in both the erect and supine positions is higher than in Group II *a*, and it is at this stage that the venous pressure rise begins to appear.

Group III. The output is now falling away towards values about half the normal, in spite of a progressive rise of the venous pressure to higher levels.

4. The significance of these findings is discussed, together with further observations on the effects of exercise and venesection. The more significant facts of cardiac behaviour in congestive failure established in this work are:

(*a*) diminution of the ability of the heart to respond to venous pressure increments, and

(*b*) the occurrence of venous congestion as a possible 'compensating' mechanism, and not as a passive phenomenon dependent on diminution of cardiac output.

This work was begun with the aid of an expenses grant from the Medical Research Council and more recently it has been financed by a grant from

the Lawrence fund of the Royal Society while I was holding the Johnston and Lawrence Research Fellowship of the Royal Society. The cases studied were usually under my care in the wards of Professor W. T. Ritchie, while Drs. W. A. Alexander and D. M. Dunlop also assisted by transferring suitable cases to me. I am especially grateful to these physicians for their valuable co-operation.

#### *Appendix of Case Records*

The following contractions are used :

A.V.O.D. = arteriovenous oxygen difference in c.c. per litre.

e = erect.

s = supine.

V.P. = Venous pressure in cm. above sternal angle.

B.P. = Arterial blood-pressure.

S.A. = Sternal angle.

#### *Group I*

*Case 1. Auriculo-ventricular heart-block of unknown etiology.* A professional man, aged 53, who had led a vigorous, active life, became aware in April 1936 that his heart was beating slowly. Electrocardiograms showed complete heart-block, with an auricular rate of 88 and a ventricular rate of 43 per minute. Since then the ventricular rate has usually ranged from 34 to 40. At the time of examination (January 1937) he was able to walk five or six miles daily with ease. B.P. 120/52. Cardio-thoracic ratio 0.48. A.V.O.D. e. 75, s. 59. V.P. 1 cm. below level of S.A.

*Case 2. Atheromatous coronary disease.* A miner, aged 57, had had an attack of pain and a feeling of tightness across the chest while at his work six weeks before admission. The pain was localized behind the sternum and since first felt had tended to recur on exertion. He was not breathless. B.P. 126/80. Apex-beat in fifth space 4 inches to left of mid-line. A systolic aortic murmur was audible. X-rays showed a heart of normal size and contour, but the aorta was diffusely enlarged and elongated. Electrocardiogram showed left bundle-branch block. A.V.O.D. e. 82.5, s. 61, 67.

*Case 3. (? Congenital) aortic stenosis.* A fisherman, aged 34, had complained of palpitation over a period of four years. B.P. was 135/75, the apex-beat  $4\frac{1}{2}$  inches to left of the mid-line in the fifth space. A systolic aortic thrill was felt, and a rough aortic systolic murmur was propagated into the vessels of the neck. Electrocardiogram showed left axis deviation and radiography showed some left ventricular hypertrophy with a cardio-thoracic ratio of 0.47. Wassermann reaction negative. A.V.O.D. e. 94, s. 64. V.P. 1 cm. below S.A.

*Case 4. Coronary thrombosis.* A commercial traveller, aged 60, had had anginal pain while climbing stairs a month before admission. Three days before admission he developed a dull praecordial ache which gradually became more severe. Apart from this he had no symptoms. B.P. 120/80. Apex felt in fifth space  $3\frac{1}{2}$  inches to left of mid-line. No murmurs. Electrocardiograms showed marked ST deviations in leads II and III, indicating posterior

coronary thrombosis. X-ray showed some elongation of the aorta. Cardio-thoracic ratio 0.41. A.V.O.D. s. 68.5.

*Case 4a. Rheumatic auricular fibrillation.* An electrician, aged 31, had been complaining of pains in the shoulders for six weeks. There was no breathlessness or oedema. B.P. 112/64, pulse-rate 80 and totally irregular. Apex-beat in fifth space 6 inches from the mid-line; systolic and diastolic murmurs audible at the apex. Electrocardiogram showed coarse fibrillation with a ventricular rate of 80 per minute. A.V.O.D. s. 67, 69, 61, 65, 67, on successive days.

*Case 5.* (Case III, 3, after digitalization and rest in bed.) The patient was fit for considerable physical exertion and could ascend two flights of stairs without undue breathlessness. A.V.O.D. e. 86, s. 63. V.P. not raised above S.A.

*Case 6.* (Case IIa, 5, after control of the pulse-rate by digitalis. Symptoms of failure had completely disappeared.) A.V.O.D. s. 60. V.P. at level of S.A.

#### Group IIa

*Case 1. Syphilitic aortitis and aortic incompetence.* A miner, aged 51, had complained of praecordial pain and breathlessness on stairs or a steep incline for one year. B.P. 140/70. Apex-beat in fifth space  $4\frac{1}{2}$  inches to left of mid-line; a double aortic murmur was audible. Wasserman strongly positive. X-rays showed diffuse dilatation of the ascending part of the aortic arch with slight hypertrophy of the left ventricle. Cardio-thoracic ratio 0.48. Electrocardiogram showed left axis deviation.

Degree of postural change estimated in this case by oxygen consumption method, see Table I.

*Case 2. Hypertensive auricular fibrillation.* A retired office worker, aged 59, had been unable to make any severe exertion for two years. On one or two occasions the ankles had swelled at night, but he was usually free from oedema. B.P. 190/110. Apex-beat in sixth space 5 inches to left of mid-line. No murmurs audible. X-ray showed enlargement of the whole heart, the cardio-thoracic ratio being 0.51. Electrocardiogram showed auricular fibrillation, left axis deviation, and inversion of T in lead I. A few crepitations were audible at the extreme bases, and the vital capacity was 2.4 litres. A.V.O.D. e. 92, s. 82, 77. V.P. not raised.

*Case 3. Rheumatic mitral and aortic disease.* A mill worker, aged 31, had been breathless on exertion for three years. The breathlessness came on only if he hurried, or ran up a flight of stairs. He was capable of walking considerable distances on the level without discomfort. He had a haemoptysis just before admission. He had had rheumatic fever on two occasions when aged 17 and 19. B.P. 115/30. Ventricular rate 78 per minute with an occasional premature beat. Apex-beat in the sixth space,  $4\frac{1}{2}$  inches to left of mid-line. Systolic and diastolic murmurs audible over the praecordium. X-rays showed enlargement of left ventricle, a prominent conus, and enlargement of left auricle. Cardio-thoracic ratio 0.52. Electrocardiogram showed slight right axis deviation. Vital capacity 2.5 litres. A.V.O.D. e. 96, s. 84. V.P. not raised.

*Case 4. Rheumatic mitral disease with auricular fibrillation.* A motor mechanic, aged 17, had become conscious of tightness in the chest four days

before admission. This feeling of discomfort was exaggerated by exertion, and he was unable to walk fast on account of shortness of breath. He was also conscious of irregular palpitation. Eight years previously he had suffered from rheumatism and chorea. B.P. 108/60. Ventricular rate 166, with a pulse deficit of 70. Apex-beat in the fifth space, 4 inches to left of mid-line. When rate was controlled, systolic and diastolic murmurs were audible at the mitral area. X-rays showed enlargement of the conus pulmonalis, and the cardio-thoracic ratio was 0.54. Electrocardiogram showed auricular fibrillation with right axis deviation. Vital capacity 3.5 litres. A.V.O.D. s. 89, e. 108, 100, 109, 100. V.P. 1 cm.

*Case 5. Rheumatic mitral and aortic disease with auricular fibrillation.* A salesman, aged 32, had gradually been compelled to reduce the amount of exercise for five or six weeks. For three weeks before admission he had noticed breathlessness on walking up a slope, but he had never had any swelling of the feet. These recent symptoms coincided with the onset of severe palpitation. He also had some praecordial pain. Ten years ago he had suffered from rheumatic fever. B.P. 110/56. Ventricular rate 168, with a pulse deficit of 56. Apex-beat in fifth space, 5 inches to left of mid-line. Systolic murmurs audible in aortic and mitral areas, with a short diastolic murmur at the latter area. X-rays showed enlargement of left auricle and conus. Cardio-thoracic ratio 0.51. Electrocardiogram showed auricular fibrillation without any definite axis deviation. A.V.O.D. e. 92, 89, s. 82. V.P. not raised.

*Case 6. Rheumatic mitral and aortic disease.* An unemployed miner, aged 23, had been conscious of palpitation on exertion since the age of 18. He had had haemoptysis on three occasions recently. He had become breathless if he tried to climb a flight of stairs quickly, but not if he took it slowly. An attempt to work as a miner recently exhausted him after a week. He also had attacks of nocturnal dyspnoea and was conscious of occasional transient pain over the praecordium. There was no oedema of the feet. History of chorea in 1923, and attacks of rheumatic fever in 1929, 1930, and 1932. B.P. 120/75. Pulse 90 to 100, regular. Apex-beat in fifth space  $5\frac{1}{2}$  inches to left of mid-line. Presystolic thrill, with presystolic, systolic, and diastolic murmurs at apex. High-pitched diastolic murmur to left of sternum. X-rays showed marked enlargement of left auricle and conus, with considerable hypertrophy of the left ventricle. Cardio-thoracic ratio 0.55. Electrocardiogram showed right axis deviation. There were medium crepitations at both bases. A.V.O.D. e. 83, s. 79. V.P. 0 to 1 cm.

#### Group II b

*Case 1. Syphilitic aortic incompetence.* A crane driver, aged 47, had suffered from pain in the chest and attacks of breathlessness on walking more than 100 yards. He had also had attacks of nocturnal dyspnoea with frothy sputum, which had been blood-stained on one occasion. He had also had some swelling of the feet at the end of the day. Wassermann reaction strongly positive. B.P. 170/30. Capillary pulsation visible. Apex-beat felt in the sixth space 6 inches to left of the mid-line. Double aortic murmur audible. X-rays showed hypertrophy of the left ventricle. Electrocardiogram showed inversion of T in leads I and II, but no left axis deviation. Crepitations were audible at both bases. Vital capacity 2.8 litres. A.V.O.D. e. 85, 77, 76, s. 74, 76. V.P. not raised.

*Case 2. Cardiovascular syphilis.* A ship's officer, aged 56, had complained of gradually increasing breathlessness for over two years. He was unable to walk more than 100 yards without breathlessness, and swelling of the feet was always present at night. Wassermann reaction strongly positive. Oedema was present affecting the legs, sacrum, and genitals. B.P. 140/90. Apex-beat felt in the sixth space  $5\frac{1}{2}$  inches to left of mid-line. No murmurs. X-rays showed nothing abnormal except slight dilatation of the heart to the left. Electrocardiogram showed left axis deviation, a P-R interval of 0.22 seconds, with an occasional dropped beat. There was some oedema at the bases of the lungs. When cardiac output studies were made there was no oedema of the limbs and he was able to walk short distances on the level without breathlessness. A.V.O.D. e. 76, 79, 77, s. 76.5, 78, 72, 73. V.P. 2 cm.

*Case 3. Rheumatic mitral disease with fibrillation.* A barber, aged 41, complained of breathlessness and tightness across the chest, which came on suddenly one afternoon a year before admission. He was breathless on walking up a flight of stairs, and preferred to be propped up in bed, as he was uncomfortable lying flat. In 1917 he had 'Trench Fever' with joint pains. B.P. 120/70. Ventricular rate 80-90 and totally irregular. Apex-beat in fifth space, 4 inches to left of mid-line. Systolic and diastolic murmurs audible at the apex. X-rays showed enlargement of conus and pulmonary artery. Cardio-thoracic ratio 0.55. Electrocardiogram showed auricular fibrillation. Lungs, no crepitations at bases. Liver not enlarged. A.V.O.D. e. 79, 79.5, s. 82, 79.5, 81, 79.1. V.P. 3 cm.

*Case 4. Hypertensive heart failure; chronic nephritis.* A retired station-master, aged 76, had complained of breathlessness and swelling of the feet for a year. He also had attacks of nocturnal dyspnoea and on some occasions had had to sit up in a chair all night. On admission he was extremely dyspnoeic and oedematous up to the sacrum. B.P. 160/95. Apex-beat in sixth space  $4\frac{1}{2}$  inches to left of mid-line. Ventricular rate was regular, about 100 per minute, and there was a systolic apical murmur. No X-ray examination was made. Electrocardiogram showed left axis deviation and splintering of QRS in all leads. Crepitations audible at both bases. Liver enlarged. Urine contained albumin and granular casts. Blood urea 64 mg. per cent. The symptoms of severe failure improved greatly with rest, and the estimations of the A.V.O.D. were carried out while he was convalescent and able to walk slowly on the level without dyspnoea, although his feet tended to swell in the evenings. A.V.O.D. e. 83, 76, s. 84, 81, 81. V.P. 4 cm.

*Case 5. Rheumatic mitral stenosis.* An unemployed man, aged 48, had had breathlessness on exertion for two years, and also swelling of the feet in the evenings for some months. Breathlessness was induced by walking quickly up one flight of stairs. Six years before admission he had had an attack of rheumatic fever; he was also the subject of epileptic fits. On admission there was slight oedema of the feet and legs. Pulse was 70 to 80 and regular. B.P. 96/60. Apex-beat felt in the fifth space,  $4\frac{1}{4}$  inches to the left of the mid-line. Presystolic, systolic, and diastolic murmurs were audible at the mitral area. Electrocardiogram showed right axis deviation. There were no accompaniments on auscultation over the lungs. The liver was not enlarged. While in hospital he lost nine pounds in weight as his oedema disappeared, the treatment being rest in bed. A.V.O.D. e. 81, 80, s. 79. V.P. 3 to 5 cm.

*Case 6. Rheumatic mitral stenosis with auricular fibrillation.* An unemployed miner, aged 37, had complained of breathlessness on exertion for four years and swelling of the ankles for two months; the latter symptom was most pronounced at the end of the day. He was made breathless by climbing one flight of stairs slowly. Recently he had 'asthmatic' attacks in the night. He was also conscious of irregular palpitation on exertion, and recently his sputum had been blood-stained on one occasion. At the age of 10 he had suffered from chorea. The lips and ears were cyanosed. Pulse 90 to 100 and irregular. B.P. 112/72. Apex-beat in fifth space  $5\frac{1}{2}$  inches to left of mid-line. Systolic and diastolic murmurs heard at the mitral area. X-rays showed gross enlargement of both auricles and right ventricle. Cardio-thoracic ratio 0.65. Electrocardiogram showed auricular fibrillation with right preponderance. Lungs showed no crepitations although the vital capacity was diminished (2.5 litres). A.V.O.D. e. 88, 84, s. 82. V.P. 1 cm.

### Group III

*Case 1. Rheumatic mitral stenosis.* A schoolboy, aged 16, had been breathless for a year, during which time he was totally incapacitated for games. For three months he had had pain in the upper abdomen and had been vomiting almost daily. He had suffered from growing pains and sore throats recently. On examination he was rather undersized, orthopnoeic, and cyanosed. B.P. 110/70. Pulse 100 to 110 and regular. Apex-beat in fifth space 4 inches to left of mid-line. Presystolic and systolic murmurs at the apex. X-rays revealed enlargement of left auricle, conus, and left ventricle. Electrocardiogram showed large P-waves and right axis deviation. Crepitations audible at the bases of the lungs. Liver enlarged 4 to 5 inches below the costal margin, nearly to the umbilicus. A.V.O.D. e. 122, 129, s. 122, 124. V.P. 4 cm.

*Case 2. Rheumatic mitral disease.* A green-keeper, aged 23, had complained of shortness of breath for six months and, more recently, swelling of the feet at night. For three weeks before admission he had been quite incapable of any physical exertion, had been having considerable pain in the upper abdomen, and had frequently vomited. The patient had had rheumatic fever eight years previously. He was orthopnoeic and breathless at rest. The cheeks and lips were cyanosed. There was gross oedema of the feet, legs, and lower part of the back, and an icteric tinge of the conjunctivae (icterus index 27). Pulse 100 to 110 and regular. B.P. 110/80. Apex-beat in sixth space  $5\frac{1}{2}$  inches to left of mid-line. Systolic and diastolic murmurs heard at the mitral area. Electrocardiogram showed right axis deviation. Crepitations audible for 1 to 2 inches above the bases of both lungs. Liver enlarged 3 to 4 inches below the costal margin. The patient was treated by rest in bed and digitalis, but he deteriorated rapidly. Auricular fibrillation began two weeks before death, but there was no response to digitalization. A.V.O.D. s. 101. V.P. 6 cm.

*Case 3. Hypertensive auricular fibrillation.* A retired violin-maker, aged 70, complained of breathlessness and swelling of the legs which had come on quite quickly in the course of a month. On admission he was unable to walk, even on the level, without extreme breathlessness. The legs, abdomen, and arms had also become swollen, in that order. On admission he was uncomfortable lying flat; oedema of the feet, legs, arms, sacrum, and genitalia was gross. Cyanosis of the lips and fingers was apparent. B.P.

135/80. (There was, however, a history of transient hemiplegia some months before, and after recovery he was found to have hypertension with a B.P. of 175/100.) Ventricular rate 160 per minute, irregular with a pronounced pulse deficit. Apex-beat in fifth space  $4\frac{1}{2}$  inches to the left of the mid-line; no murmurs. X-rays (after recovery) showed slight left ventricular hypertrophy, the cardio-thoracic ratio being 0.49. Crepitations were audible up to the middle of the scapulae. The patient recovered completely from this state of severe congestive failure on control of the ventricular rate by digitalis. A.V.O.D. s. 138, 124. V.P. 11 cm. (before digitalization).

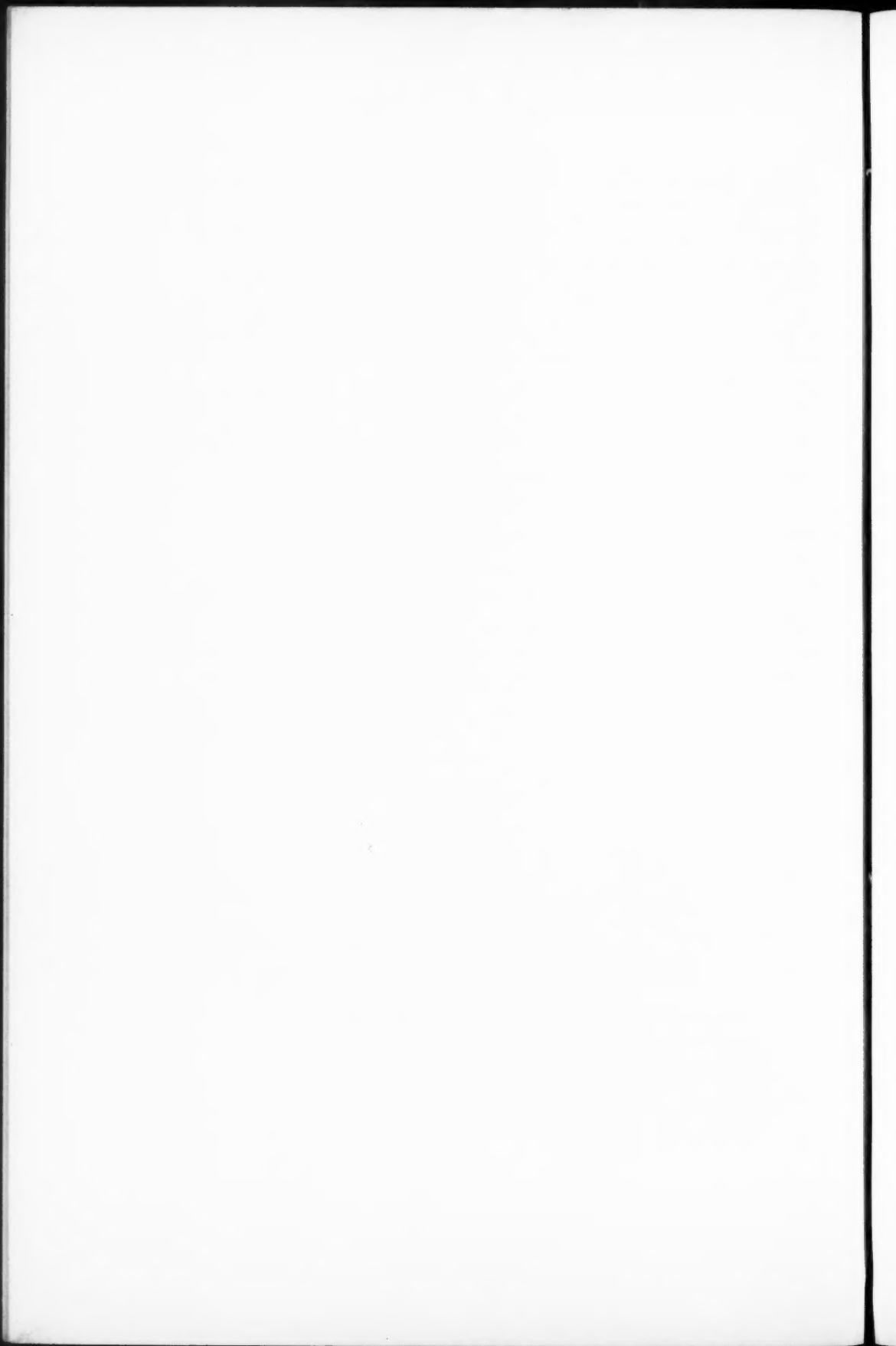
*Case 4. Coronary atheroma and congestive heart failure.* A factory stoker, aged 57, had had breathlessness on exertion for twelve months, especially on going up a slight incline. The feet and legs were swollen at the end of a day's work. He had also had a troublesome cough with frothy sputum. Recently he had become breathless at rest, and, in addition, had paroxysms of acute breathlessness coming on at any time in the twenty-four hours. While in the ward he had occasional attacks of substernal pain. The patient was pallid, with cyanosis of the lips and nails, and was orthopnoeic. Oedema was present affecting the feet, legs, and sacrum. Pulse 100 to 110 and regular with occasional extra-systoles. B.P. 125/90. Apex-beat felt in fifth space 4 inches to left of mid-line. No murmurs audible. X-rays showed considerable hypertrophy of the left ventricle, the cardio-thoracic ratio being 0.58. Electrocardiograms showed ventricular extrasystoles, slight left axis deviation, and in the chest leads there was a deep Q and high take-off of T, suggesting anterior coronary infarction. Crepitations were heard over the lungs up to the angles of the scapulae. Liver not enlarged. A.V.O.D. s. 153 (a week later 119). V.P. 4 to 5 cm.

*Case 5. Rheumatic mitral stenosis.* A bookbinder, aged 40, had complained of breathlessness and cough with frothy sputum for two or three years. The breathlessness was at first only noticeable during heavy work, but recently it had been appearing on the slightest exertion. Two weeks before admission the legs began to swell and the swelling extended up to the abdomen. He had also had severe attacks of nocturnal breathlessness recently. No previous history of rheumatism, but had had scarlatina when aged 13. The patient was breathless at rest, with cyanosis of lips and fingers, and oedema of the feet, legs, sacrum, and arms. Pulse 108, regular. B.P. 110/72. Apex-beat in fifth space 4 inches to left of mid-line. Pre-systolic, systolic, and diastolic murmurs audible at the mitral area. Electrocardiograms of low voltage showed right axis deviation and broad forked P-waves. Crepitations audible up to the middle of the scapula. The liver was enlarged 3 to 4 inches below the costal margin, and there was definite ascites. Patient deteriorated slowly and died nine weeks after admission. A.V.O.D. s. 138. V.P. 13 cm. After venesection of 1 litre, A.V.O.D. s. 153. V.P. 7 cm.

*Case 6. Hypertensive auricular fibrillation.* An engineer, aged 64, had complained of breathlessness on exertion for two months, and lately his feet had become swollen after walking. On examination he was breathless even in bed. There was cyanosis of the lips and ears, with oedema of the feet, legs, and sacrum. Ventricular rate 130, irregular rhythm, pulse deficit 30. B.P. 168/110. Apex-beat felt in fifth space 4 inches to left of the mid-line. Considerable improvement resulted from digitalization, but cerebral arteriosclerosis led to some mental deterioration. A.V.O.D. s. 156. V.P. 10 cm.

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## THE CLINICAL VALUE OF THE ESTIMATION OF LAEVULOSE TOLERANCE BY MEANS OF ANALYSES OF BLOOD-LAEVULOSE<sup>1</sup>

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THE method usually employed for the estimation of laevulose tolerance, as a test of hepatic function, is that introduced by Schirokauer (1913). It depends on the estimation of total blood-sugar after the ingestion of laevulose. Normally there is only a slight rise in blood-sugar, and this is explained on the theory that laevulose reaching a normal liver by the portal vein is largely transformed to glycogen, so that very little passes through the liver to reach the general circulation. Abnormally high rises are attributed to failure of the liver to absorb the incoming laevulose at a normal rate. No distinction is made between blood-glucose and blood-laevulose; it has been assumed that the increment in total blood-sugar is due to the presence of laevulose. The use of this test for the estimation of liver function has been criticized on the ground that damage to the liver may not be the only factor capable of causing abnormal results. Other factors which must be considered are the rate of absorption of the sugar, and the part played by tissues other than the liver in removing laevulose from the circulation. These points will be dealt with in due course. A more serious objection to the test in its usual form is the use of total blood-sugar estimations. Variations in blood-glucose may mask the changes due to the presence of laevulose in the circulation. There is also the technical difficulty that in determining the rise in total sugar above the fasting level, it is necessary to estimate a small increment on a large total amount, and the estimation of the increment is liable to a summation of the errors in the determinations of total sugar.

Various methods are available for the determination of laevulose, and in recent years two methods have been developed which make it possible to apply blood-laevulose analyses to clinical work. Van Creveld introduced a colorimetric method based on the blue colour obtained when laevulose is heated with diphenylamine in acid solution. This principle has been used by Radt (1928) and Corley (1929), and Radt's method has been modified by

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Patterson (1935). A method based on the red colour obtained when laevulose is heated with sodium tauroglycocholate and hydrochloric acid has been developed by Scott (1935 *a*). Patterson found that his method and Scott's gave concordant results. Scott (1935 *b*) has applied his method to the estimation of laevulose tolerance, and has found that estimations of blood-laevulose are much more satisfactory than estimations of total sugar. He found a narrower normal range, and a clearer distinction between normal and abnormal results. Variations in glucose caused little interference with the estimation of laevulose, and in pancreatic diabetes without liver disease, the blood-laevulose curve was normal, although the total blood-sugar curve after the ingestion of laevulose was greatly raised and prolonged.

In view of these results it seemed desirable to re-investigate the value of the laevulose tolerance test as a measure of hepatic function, using estimations of blood-laevulose, and the present work was undertaken with that object. In selecting cases, we have included a number in which the condition of the liver was uncertain when the patients were first seen, because it is in just such cases that a laboratory aid to diagnosis is required. The later history of these patients was followed, often with repeated laevulose tolerance tests, until the diagnosis could be established. In all cases the diagnosis has been based on the clinical course of the disease, or on observations made at operation or post-mortem examination, and has been independent of the results of laevulose tolerance tests.

#### *Methods*

Laevulose was given, usually after a night's fast, and never less than four and a half hours after the previous meal. The dose was for adults 50 gm., and for children 1 gm. per kg. body-weight. Oxalated venous blood was collected before the ingestion of laevulose and at one hour and two hours later. The blood-laevulose was estimated by Patterson's method. The method does not give true proportionality of colour to concentration, and it is necessary either to work with standard laevulose solutions of concentrations close to those of the samples analysed, or to make corrections for the departure from proportionality. In analysing samples of blood taken in the fasting state, some colour was always obtained, but it was difficult to estimate, partly because of its faintness, and partly because the tint was greenish-blue and could not be accurately matched against the purplish-blue colour given by standard laevulose solutions. If the intensity of the colour is estimated as nearly as possible and expressed in terms of laevulose, the figures for normal subjects range from 3 to 7 mg. per 100 c.c. These figures certainly do not represent laevulose. It has been found that glucose gives a slight colour under the conditions of the method. Glucose corresponding to 100 mg. per 100 c.c. of blood gives an apparent laevulose figure of about 3 mg. per 100 c.c. Probably the colour obtained in analysing blood in the fasting state is due to a mixture of a trace of blue, due to glucose, with a trace of yellowish colour yielded by the reagents, or substances in the blood filtrates. Experiments with laevulose added to blood showed that the colour derived from the blood alone contributes to the total colour

obtained when laevulose is added, and in order to obtain consistent results for the recovery of laevulose added to blood, it is necessary to take into account the figure for the blood alone.<sup>2</sup> For this reason it was decided that in recording the results for blood-laevulose curves the colour obtained from 'fasting' blood should be expressed as laevulose, and this figure used as a basis for estimating the rise in blood-laevulose in the later specimens. The figures given for the fasting blood-laevulose are not intended as true laevulose analyses.

### Results

*Normal subjects and non-hepatic diseases.* The findings in thirteen normal subjects are given in Table I. The apparent blood-laevulose in the fasting state ranged from 3 to 7 mg. per 100 c.c. The peak reached in normal subjects ranged from 6 to 21 mg. per 100 c.c., and the rise above the apparent initial level ranged from 3 to 15 mg. per 100 c.c. On only one occasion was the rise greater than 10 mg. per 100 c.c., namely in Case 13, and a repetition of the test gave a result in the same range as in the remainder of the normal subjects.

TABLE I  
*Normal Subjects*

Case.	Blood-laevulose mg. %			
	Before.	1 hr.	2 hrs.	Rise.
1	Trace	8	3	8
2	5	12	13	8
3	6	13	9	7
4	8	12	9	4
5	4	8	6	4
6	3	6	5	3
7	6	12	7	6
8	6	12	7	6
9	4	11	6	7
10	5	11	9	6
11	6	12	12	6
12	7	17	15	10
13 (a)	6	21	10	15
13 (b)	5	8	7	3

The findings in nineteen patients without liver disease are given in Tables II and III. In only one of these was an abnormal result obtained (Case 18). This patient had *tabes dorsalis*, but there was no evidence that

<sup>2</sup> Both in experiments with laevulose added to blood, and in work with pure laevulose solutions, we have found considerable technical irregularity in Patterson's method. The great majority of the analyses, however, are correct within  $\pm 2$  mg. per 100 c.c. of blood, and the technical error does not invalidate the main conclusions of the present work. Recently a new modification of the diphenylamine method has been developed by one of us (F. K. H.) and so far as present experience goes, the new method gives greater accuracy than the old, and eliminates the effect of interfering colours, except for the slight trace of colour given by glucose. The new method also takes much less time and is more convenient for routine analyses (Herbert, 1938).

the syphilis had affected the liver. On re-examination six months later, the laevulose tolerance was normal. A patient who had had a gastro-enterostomy performed was included, because in such a case abnormally rapid absorption of sugar might be expected (Case 17). The blood-laevulose curve fell within the normal range. Pancreatic disease did not affect the

TABLE II  
*Non-hepatic Diseases*

Case.	Diagnosis.	Date.	Blood-laevulose mg. %				Confirmation of diagnosis.
			Before.	1 hr.	2 hrs.	Rise.	
14	Hypochromic anaemia	—	9	16	8	7	Clinical data
15	Hypochromic anaemia	—	5	11	8	6	" "
16	Carcinoma of ovary	—	4	8	7	4	Operation
17	Gastro-enterostomy	—	6	10	15	9	" "
18	Tabes dorsalis	29.8.36	7	21	41	34	Clinical data
		12.2.37	4	10	10	6	
19	Post-haemorrhagic anaemia	26.5.36	3	4	6	3	" "
		1.10.36	5	10	8	5	
20	Bronchitis and emphysema	—	8	13	8	5	" "
21	Thrombosis of inferior vena cava	—	10	17	13	7	" "
22	Megalocytic anaemia during pregnancy	—	5	10	8	5	" "
23	Chronic encephalitis. Parkinson's syndrome	—	4	8	10	6	" "
24	Hydronephrosis	—	6	18	10	12	Operation
25	Cerebral thrombosis	—	5	15	15	10	Clinical data
26	Polycythaemia vera	3.6.36	4	12	6	8	" "
		10.2.37	5	12	7	7	
27	Gastric ulcer	—	6	10	9	4	" "
28	Dyspepsia	—	5	15	8	10	" "
29	Acute pancreatitis	—	4	7	6	3	Operation

TABLE III

Case.	Diagnosis.	Blood-laevulose mg. %.				Total blood-sugar mg. %.			
		Before.	1 hr.	2 hrs.	Rise.	Before.	1 hr.	2 hrs.	Rise.
30	Diabetes mellitus	8	11	21	13	292	310	380	88
31	Diabetes mellitus	9	17	13	8	328	424	420	96
32	Diabetes mellitus	16	28	28	12	400	440	460	60

laevulose tolerance as determined by blood-laevulose estimations. One patient with acute pancreatitis gave a normal result (Case 29). Three patients with diabetes mellitus and without hepatic disease (Table III) showed only normal rises in blood-laevulose, although the figures for total blood-sugar showed that the administration of laevulose to diabetic patients caused a considerable rise in blood-glucose. As has been mentioned, glucose gives a slight colour with diphenylamine, and the increase in blood-glucose in these cases would cause an apparent rise in laevulose of about 2 mg.

per 100 c.c. The blood-laevulose figures have not been corrected for the effect of glucose, but even without correction they fall within the normal range.

Taking together the whole series of normal subjects and patients without hepatic disease, we have 32 cases. If we exclude the aberrant result in Case 18 (which may possibly have been due to unsuspected syphilitic disease of the liver), we find that the rise of blood-laevulose above the apparent initial level is never greater than 15 mg. per 100 c.c., and that rises greater than 10 mg. per 100 c.c. occur in only four cases out of the 32. We therefore take a rise of up to 10 mg. per 100 c.c. as definitely normal, and a rise in the range of 11 to 15 mg. per 100 c.c. as a 'high normal' result.

*Diseases of the liver.* The results for various hepatic diseases are given in Table IV. Various types of hepatitis are illustrated by Cases 33 to 39. In two of these, namely Cases 35 and 36, the jaundice was already diminishing at the time of the test, and the laevulose tolerance was normal. The other five cases all showed deficient tolerance during the attack of hepatitis, and in two cases re-examined after recovery the return to a normal curve was observed (Cases 33 and 38). Case 38 is an example of catarrhal jaundice associated with diabetes, and shows that the use of blood-laevulose estimations makes it possible to distinguish between hepatic and pancreatic insufficiency. During the attack of jaundice the results were:

	Blood-laevulose <sup>3</sup> (mg. per 100 c.c.).	Total blood-sugar (mg. per 100 c.c.).
Before laevulose	10	320
1 hr. after	34	440
2 hrs. after	21	440

After recovery from the jaundice the blood-laevulose curve returned to normal, and the total blood-sugar curve still showed the typical diabetic result:

	Blood-laevulose <sup>3</sup> (mg. per 100 c.c.).	Total blood-sugar (mg. per 100 c.c.).
Before laevulose	8	340
1 hr. after	14	460
2 hrs. after	14	400

Two cases of subacute liver atrophy have been studied (Cases 40 and 41). In Case 40, the first laevulose tolerance test was performed ten weeks after the onset of symptoms, and showed a 'high normal' result. Three months later, the laevulose tolerance had become deficient. The patient died seven weeks after the second test. In Case 41, there was subacute atrophy with post-atrophic fibrosis, and the laevulose tolerance was deficient.

In Case 42, there was obstructive jaundice due to pancreatitis. The patient was examined first in November 1935 during an attack of jaundice, and had a deficient laevulose tolerance. He recovered, and was seen again in September 1936, when he appeared quite well and was found to have

<sup>3</sup> The figures are not corrected for the slight effect of glucose on the apparent laevulose figures, but the effect is too small to affect the interpretation of the results.

TABLE IV

*Diseases of the Liver*

Case.	Diagnosis.	Date.	Van den Bergh reaction.	Blood-lævulose mg. %				Confirmation of diagnosis.
				Before.	1 hr.	2 hrs.	Rise.	
33	Hepatitis. In attack	12.4.37	—	7	27	12	20	Clinical data
	Hepatitis. After recovery	27.5.37	Negative	8	12	11	4	
34	Toxic hepatitis after anti-syphilitic treatment	2.12.36	38 units. Direct	6	23	12	22	Clinical data
35	Weil's disease (recovering)	22.4.36	—	6	10	6	4	Positive agglutination tests. Spirochaetes found in urine
36	Catarrhal jaundice (recovering)	23.3.37	24 units. Direct	7	15	10	8	Clinical data
37	Catarrhal jaundice	1.3.37	20 units. Direct	5	41	25	36	Clinical data
38	Catarrhal jaundice and diabetes: In attack	22.4.37	16 units. Direct	10	34	21	24	Clinical data
	After recovery from jaundice	13.5.37	2 units. Mixed	8	14	14	6	
39	Weil's disease	31.12.37	—	5	22	12	17	Agglutination test
40	Subacute atrophy of liver	28.4.37	40 units. Direct	4	17	10	13	Microscopic examination of biopsy specimen
		15.7.37	47 units. Direct	3	25	30	27	
41	Post-atrophic fibrosis of liver following treatment of polycythaemia with phenylhydrazine	7.6.37	2 units. Indirect	7	29	11	22	Post mortem
42	Chronic pancreatitis; Obstructive jaundice	27.11.35	40 units. Direct	7	34	10	27	Operation
		9.9.36	2 units. Indirect	5	15	11	10	
		31.12.37	—	4	36	11	32	
43	Portal cirrhosis of liver	23.4.37	0.6 units. Indirect	6	11	7	5	Biopsy three years earlier
44	Carcinoma of ampulla of Vater. Slight hepatic cirrhosis	2.11.36	28 units. Direct	6	20	11	14	Operation
45	Portal cirrhosis	2.4.37	0.6 units. Indirect	5	23	13	18	Post mortem
46	Portal cirrhosis (alcoholic)	15.10.36	—	6	18	18	12	Clinical data
47	Portal cirrhosis (alcoholic)	26.2.37	—	6	25	17	19	Post mortem

TABLE IV (continued)

Case.	Diagnosis.	Date.	Van den Bergh reaction.	Blood-laevulose mg. %				Confirmation of diagnosis.
				Before.	1 hr.	2 hrs.	Rise.	
48	Portal cirrhosis of liver	15.5.37	4 units. Indirect	5	18	10	13	Clinical data
		21.7.37	—	7	25	25	18	
49	Syphilitic cirrhosis with portal obstruction, and gumma of sternum	24.5.37	1 unit. Indirect	10	14	11	4	Clinical data
50	Portal cirrhosis	4.12.35	—	trace	17	11	(17)	Clinical data
		23.9.36	—	7	28	11	21	
51	Cirrhosis	18.3.37	4 units. Mixed	5	19	19	14	Clinical data
		22.6.37	10 units. Direct	6	23	32	26	
52	Portal cirrhosis	20.7.37	24 units. Direct	6	24	15	18	Operation (omenterectomy)
53	Portal cirrhosis	3.3.37	—	5	15	14	10	Clinical data
54	Gallstones; early biliary cirrhosis of liver	13.4.37	11 units. Direct	6	19	12	13	Operation
55	Secondary carcinoma of liver (primary in gall-bladder)	21.7.37	30 units. Direct	10	17	11	7	Post mortem
56	Secondary carcinoma of liver (primary in stomach)	24.3.37	40 units. Direct	6	30	11	24	Clinical data
57	Carcinoma of liver	25.7.36	—	5	24	11	19	Clinical data
58	Carcinoma pancreas (secondary in liver)	2.6.37	40 units. Direct	5	7	7	2	Post mortem
59	Carcinoma of liver	15.1.37	4 units. Mixed	6	24	19	18	Operation; biopsy of liver
60	Secondary carcinoma of liver (primary in stomach)	25.3.37	40 units. Direct	5	21	21	16	Clinical data
61	Carcinoma of pancreas and hepatomegaly	9.7.36	—	5	24	14	19	Operation
62	Carcinoma of pancreas and hepatomegaly	20.7.37	26 units. Direct	9	28	12	19	Clinical data
71	Lymphadenoma with local infiltration of liver	24.1.36	—	6	15	13	9	Post mortem
		27.6.36	—	5	14	10	9	
		4.9.36	1 unit. Indirect	10	15	11	5	
73	Haemochromatosis	—	—	—	28	14	(28)	Post mortem
74	Haemochromatosis with diabetes	—	—	8	32	19	24	Clinical data

a normal laevulose curve. In December 1937 he was examined during another attack of jaundice, and again showed a deficient laevulose tolerance. Shortly afterwards a laparotomy was performed, at which the diagnosis of pancreatitis was made. The liver was enlarged but not otherwise abnormal.

The series includes 12 cases of cirrhosis of the liver (other than the cirrhosis of Banti's disease which is considered later). In two of these (Cases 44 and 54), the cirrhosis was the result of chronic biliary obstruction; the cirrhosis was slight in degree, and was discovered at operation. In both these cases there was a 'high normal' blood-laevulose curve. In the other ten cases there were well-marked clinical signs of cirrhosis, with gross portal obstruction. Six of these 10 cases showed an abnormal laevulose tolerance at some stage of the disease (Cases 45, 47, 48, 50, 51, and 52). In two of them (Cases 48 and 51) the abnormality in laevulose tolerance developed while the patients were under observation. In Case 48 there was gross portal obstruction before the blood-laevulose curve became abnormal. In Case 51, the patient when first seen had gross hepatic enlargement with some distended abdominal veins, but no ascites; at this time the blood-laevulose curve was a 'high normal'. Three months later, he showed jaundice and ascites and the laevulose tolerance showed a marked deficiency. In four cases normal or 'high normal' blood-laevulose curves were associated with clinical signs of cirrhosis (Cases 43, 46, 49, and 53). In two of these, however, there had been clinical improvement over a long period before the laevulose tolerance was estimated (Cases 43 and 53). In Case 43, an omentopexy had been performed three years earlier, and the ascites had greatly diminished after operation. In Case 53, the patient had had ascites of diminishing degree for eight years. But diminution of the severity of the portal obstruction is not necessarily associated with good laevulose tolerance; in Case 50 there was improvement in the patient's general condition, and diminution in ascites, over a period of two years, although the laevulose tolerance was deficient.

In six cases there was malignant disease of the liver (Cases 55 to 60). Of these, two showed normal laevulose curves, and the remainder deficient tolerance. It happened that post-mortem observations were made in the two cases in which the laevulose tolerance was normal; in both there were local secondary deposits in the liver without gross destruction of hepatic tissue. In the other cases the extent of the hepatic disorganization is unknown.

In Cases 61 and 62 there was carcinoma of the pancreas with obstructive jaundice, and enlargement of the liver with distension of the gall-bladder. It is not known whether the hepatic enlargement was due to cirrhosis, to secondary malignant disease, or to distension. Both showed a slightly deficient laevulose tolerance.

Two cases of haemochromatosis have been studied. One of these, Case 73, had not reached the diabetic stage; in the other case there was diabetes.

Both showed a deficient laevulose tolerance. The relation between the blood-laevulose and the total blood-sugar was as follows:—

		Before laevulose.	1 hr. after.	2 hrs. after.
Case 73.	Blood-laevulose, mg. %	—	28	14
	Total blood-sugar, mg. %	68	100	49
Case 74.	Blood-laevulose, mg. %	8	32	19
	Total blood-sugar, mg. %	220	340	340

In Case 73, the rise in laevulose accounted for almost all the increment in total sugar. This patient was not diabetic. In Case 74, there was diabetes, and the results illustrate the independence of the blood-laevulose and blood-glucose curves. The rise in blood-laevulose is abnormally high, but is very much less than the rise in blood-glucose.

In Case 71, the association of anaemia, enlargement of the liver and spleen, and ascites suggested a diagnosis of Banti's disease with hepatic cirrhosis. The blood-laevulose curve was consistently normal over a period of seven months, and at the post-mortem examination the patient was found to have lymphadenoma with local infiltration of the liver, but without any extensive damage to the hepatic parenchyma.

We have examined one case of von Gierke's disease (Case 72, Table V). A clinical report of this case has already been published by McKeon (1937). The fasting blood-sugar showed the hypoglycaemia characteristic of the condition. After the ingestion of laevulose the blood-laevulose showed no abnormal increase, but there was a considerable rise in blood-glucose—indeed the total blood-sugar curve after the ingestion of laevulose was very similar to that obtained when glucose was given. Since in von Gierke's disease the liver is loaded with glycogen, one would not expect any failure in the ability of the liver to form glycogen from laevulose, and the normal blood-laevulose curve bears this out. The total blood-sugar curve would in this case have given a false picture of the laevulose tolerance.

*Splenic anaemia and Banti's disease.* In splenic anaemia a test of hepatic function would be very valuable if it were capable of detecting involvement of the liver in advance of the development of the symptoms and signs of hepatic disease. In Table VI are presented the results of the laevulose tolerance test in eight cases of splenic anaemia—two in which the liver was known to be normal, three in which there was cirrhosis, and three in which the condition of the liver was uncertain on the clinical evidence. In the first two cases (Cases 63 and 64) the laevulose tolerance curve was normal; in these splenectomy was performed and the liver was found normal at operation. The results in the three cases of hepatic cirrhosis show that a deficiency in laevulose tolerance does not necessarily precede the clinical evidence of liver disease. This is in accordance with the results already described in other types of hepatic cirrhosis. In Case 65, the laevulose tolerance was normal. In Case 66, a normal result was obtained at the first test, although symptoms of ascites had been developing for three months. Seven months later a deficiency in laevulose tolerance had developed. In

TABLE V

(Case 72. *Von Gierke's Disease.*)

Sugar given.	Blood-laevulose mg. %.			Total blood-sugar, mg. %.				
	Before.	1 hr.	2 hrs.	Before.	$\frac{1}{2}$ hr.	1 hr.	$1\frac{1}{2}$ hrs.	2 hrs.
Laevulose	5	8	14	40	—	75	—	105
Glucose	—	—	—	37	100	55	105	100

The blood analyses after the dose of laevulose were made on venous blood, and are likely to give lower results than would have been found for cutaneous capillary blood. The blood-sugar figures after giving glucose were obtained with cutaneous blood.

TABLE VI

*Splenic Anaemia and Banti's Disease.*

Case.	Diagnosis.	Date.	Blood-laevulose mg. %.			
			Before.	1 hr.	2 hrs.	Rise.
63	Splenic anaemia, normal liver	1.3.37	5	10	9	5
64	Splenic anaemia, normal liver	5.1.37	4	13	14	10
65	Splenic anaemia, hepatic cirrhosis	24.6.37	7	17	14	10
66	Splenic anaemia, hepatic cirrhosis	9.4.37 27.10.37	4 6	12 30	14 28	8 24
67	Splenic anaemia, hepatic cirrhosis	28.8.36 6.7.37	8 4	18 23	27 9	19 19
68	Splenic anaemia, liver condition unknown	21.11.36 17.12.36 2.7.37	4 6 5	13 27 19	— 27 15	9 21 14
69	Splenic anaemia, liver condition unknown	24.4.36 22.9.36 27.9.37	4 4 6	20 23 24	17 18 10	16 19 18
70	Splenic anaemia, liver condition unknown	4.12.35 18.9.36 7.7.37 7.12.37	Trace 5 8 4	21 19 20 19	11 12 17 14	(21) 14 12 15

TABLE VII

Number of observations in which the rise in blood-laevulose was in the range:

	Under 10 mg. per 100 c.c.	11 to 15 mg. per 100 c.c.	16 to 20 mg. per 100 c.c.	Over 20 mg. per 100 c.c.
Normals and non-hepatic diseases	36	4	—	1
Hepatitis or liver atrophy	—	1	1	8
Cirrhosis of liver	5	7	4	2
Carcinoma of liver	2	—	5	1
Haemochromatosis	—	—	—	2
Total liver diseases <sup>4</sup>	7	8	10	13

<sup>4</sup> Cases 35 and 36 are excluded because they were examined during recovery, and Cases 71 and 72 because of their special features.

Case 67, the laevulose tolerance was deficient when the patient was first seen, and remained so. Of the three cases in which the condition of the liver was uncertain on clinical evidence, one showed consistently a slight deficiency in laevulose tolerance (Case 69). The other two (Cases 68 and 70), each showed a definite deficiency on one occasion only.

It seems that in splenic anaemia the finding of an abnormal laevulose curve may sometimes be of assistance in detecting liver damage, but a normal result does not exclude cirrhosis.

### *Summary of Results*

The results are summarized in Table VII, in which the observations are classified according to the maximum rise of blood-laevulose above the initial level. Of 41 observations in subjects without hepatic disease, 36 showed rises not greater than 10 mg. per 100 c.c. Four results showed rises in the range 11 to 15 mg. per 100 c.c., and two of these were diabetics; in these two cases the rises in blood-glucose would cause the rise in laevulose to be slightly over-estimated. Only one curve was definitely abnormal, namely that of case 18—a case of syphilis in which there may possibly have been unsuspected liver damage. Although the full normal range must be taken to include rises up to 15 mg. per 100 c.c., it is evident that figures in the 'high normal' zone of 11 to 15 mg. per 100 c.c. are only rarely met with in the absence of liver disease.

Of 38 observations in liver disease, only seven fall in the usual normal range; eight give 'high normal' results, and the remaining 23 show varying degrees of deficiency. The normal and 'high normal' results are met with mainly in hepatic cirrhosis and carcinoma of the liver—conditions which are compatible with the presence of a considerable amount of normally functioning liver tissue. The results demonstrate that deficiencies in laevulose tolerance occur in a large proportion of patients with liver disease, and (with the possible exception of Case 18) are not met with in other diseases.

### *Discussion*

The physiological basis of the laevulose tolerance test will first be considered. It is a well-established fact that the liver is able to take up laevulose and convert it into glycogen. Cori (1926) compared the rates of formation of liver glycogen during the absorption of glucose and laevulose. The rate of formation of glycogen was the same for both sugars, but the rate of absorption of laevulose was only half the rate of absorption of glucose, so that the proportion of the absorbed sugar which appeared as liver glycogen was much greater in the case of laevulose than in the case of glucose. The importance of the action of the liver in removing laevulose from the blood

is also shown by the results of Cori and Cori (1927). They found that laevulose is utilized far more rapidly when injected into the portal circulation than when injected into the systemic circulation, and that the rate of utilization when the sugar is given by the portal route is much the same as the normal rate of absorption from the intestine. Both oxidation and glycogen formation in the liver contribute to this utilization of laevulose. These findings explain the normal blood-sugar curves obtained after giving glucose or laevulose. In the case of glucose, the rate of removal is slower than the rate of absorption, and the blood-sugar rises. In the case of laevulose, utilization keeps pace with absorption and there is little rise in either blood-laevulose or total blood-sugar.

The liver therefore plays a part in the removal of laevulose from the blood, but it is necessary to consider the possible rôle of other tissues. The work of Bollman and Mann (1931) shows that laevulose can be transformed to glucose in the absence of the liver, and that the glucose is then available for the relief of hypoglycaemia and the formation of muscle glycogen. The change from laevulose to glucose occurs in the stomach and intestines; the other tissues (e.g. muscles) cannot utilize laevulose directly. The only tissues concerned in the initial change of laevulose to glucose are the liver and the gastro-intestinal tract. There is other evidence of the inability of certain tissues to utilize laevulose directly. For example, Gaddie and Stewart (1934) showed that the heart-muscle cannot utilize laevulose, and Ashford (1933) showed that brain tissue formed very little lactic acid from laevulose, as compared with the lactic acid formation from glucose. There is also evidence that the pancreas is not concerned in the first stage of laevulose metabolism, namely the formation of glucose. Davidson, Kermack, Mowat, and Stewart (1936) showed that the level of blood-laevulose is independent of pancreatic control. They found that when laevulose and insulin were injected simultaneously into rabbits, the rate of removal of laevulose from the blood was no greater than when laevulose alone was given. The results of blood-laevulose curves in diabetes establish the same conclusion. It has been shown by Scott (1935, *b*), by Stewart, Scarborough and Davidson (1937), and in the present paper, that the administration of laevulose to diabetic patients causes no abnormal rise in the blood-laevulose, though it does lead to a great rise in blood-glucose. In diabetes, the first stage of transformation of laevulose to glucose or glycogen proceeds normally, but the glucose formed accumulates in the blood in exactly the same way as when glucose is given. The present paper also includes a case of acute pancreatitis, in which the blood-laevulose curve was normal.

The changes in blood-glucose which follow the administration of laevulose are of interest both from the physiological standpoint and because of their effect on the interpretation of the results of laevulose tolerance tests carried out by the older method of estimating blood-sugar. Davidson, Kermack, Mowat, and Stewart (1936) have shown that if glucose is given by mouth, and laevulose is subsequently injected at a time when the blood-sugar is

still rising, the injection of the laevulose causes a rapid fall in blood-glucose. They attribute this to stimulation of the pancreas. Stewart, Scarborough, and Davidson (1937) have pointed out that when laevulose is given by mouth, the blood-glucose usually falls slightly, and that the total blood-sugar curve is the resultant of a slight fall in glucose and a slight rise in laevulose. On the other hand, laevulose may cause a rise in blood-glucose, especially if the fasting level is low. The work of Bollman and Mann, already referred to, shows that laevulose will relieve the hypoglycaemia of hepatectomized animals, if sufficient time is allowed for the change from laevulose to glucose. The case of von Gierke's disease described in the present paper illustrates the same effect; the administration of laevulose raised the total blood-sugar from a fasting level of 40 mg. per 100 c.c., to a level of 105 mg. per 100 c.c., the greater part of the increase being due to glucose. The results are intelligible on the ground that laevulose is first changed to glucose, and that the effect on blood-glucose depends on the physiological balance at the moment. If the initial blood-glucose is low, it will rise; if it is high and the pancreas is normal, the normal regulation will come into play, but if the insulin mechanism is deficient the blood-glucose will rise.

The change from laevulose to glucose might occur with or without the intermediate formation of glycogen. The results in our case of von Gierke's disease suggest that it may occur directly. If, in von Gierke's disease, glycogen were first formed, one would expect that the newly formed glycogen would remain immobilized in the liver, since in this disorder glycogen is not mobilized in the normal way. If this occurred, one would not expect a rise in blood-glucose after giving laevulose. Since the rise occurs, it is probable that the glucose has been formed from laevulose directly, either in the liver or in the gastro-intestinal tract. Since the administration of laevulose has a variable effect on blood-glucose, according to the physiological balance at the moment, it is evident that the estimation of total blood-sugar is unsatisfactory as a method of estimating laevulose tolerance. Variations in blood-glucose mask the changes in blood-laevulose when total sugar is estimated, and may cause misleading results. When blood-laevulose is estimated, pancreatic disease and other conditions affecting the blood-glucose do not interfere with the results. It becomes possible to demonstrate a deficient laevulose tolerance in liver disease occurring in diabetic patients. This is illustrated by a case reported by Scott (1935 *b*) in which acute yellow atrophy occurred in a diabetic, and also in two of the writers' cases—namely one case of haemochromatosis with diabetes, and one of catarrhal jaundice in a diabetic.

Most of the objections which have been made to the principle of the laevulose tolerance test are removed by the use of blood-laevulose estimations, since the only organs, other than the liver, which may affect the level of blood-laevulose are the stomach and intestines. There remains the difficulty that abnormal function of the gastro-intestinal tract might affect the blood-laevulose curve. Failure in the normal mechanism of transformation

of laevulose to glucose in the intestine is a theoretical possibility, but there is no evidence that this occurs in disease. Changes in the rate of absorption are a more likely source of confusion. An abnormally rapid absorption might upset the normal balance between utilization and absorption, and cause abnormally high blood-laevulose curves. This question requires further study. The present series of observations includes one case of gastro-enterostomy; here one might expect abnormally rapid absorption, but the blood-laevulose curve was normal. Another objection to the principle of the laevulose tolerance test arises from the work of Bollman and Mann (1931), who found that in hepatectomized animals the rate of removal of injected laevulose from the blood was only slightly slower than in the normal animal. But under the conditions of parenteral administration, the liver probably plays a relatively smaller part in the removal of laevulose than when oral administration is employed. It has already been pointed out that laevulose is more rapidly utilized when given by the portal route than when injected into the general circulation. Moreover, when laevulose is injected, the blood-laevulose immediately after injection will be very high, and diffusion of laevulose from the blood to the tissue fluids is likely to play a large part in its removal. Under the conditions of the clinical test, with oral administration of laevulose, the function of the liver is probably the only important factor in determining the type of blood-laevulose curve obtained. The close association between deficient laevulose tolerance and disease of the liver, which has been found in the present work and that of others, strongly supports this view.

We must now consider more fully the work of Scott (1935 *b*) and of Stewart, Scarborough, and Davidson (1937). These authors have also applied blood-laevulose analyses to the estimation of laevulose tolerance, and their main conclusions agree with those of the present writers. There are, however, discrepancies in the normal standards adopted, which may be due to differences in technique. Scott's results were obtained by his own method. He found that in six normal subjects, laevulose was absent from the blood in the fasting state, and that the peak attained after the ingestion of laevulose was not greater than 11 mg. per 100 c.c. In these normal subjects he found that the figure obtained half an hour after the dose of laevulose was never greater than that obtained at one hour, and regarded the estimation at the half-hour point as unnecessary. The peaks of blood-laevulose in liver diseases ranged from 12 to 18 mg. per 100 c.c. Stewart, Scarborough, and Davidson (1937) have recently published a short preliminary series of blood-laevulose curves in normal and pathological cases, using Patterson's method in a modified form. Their usual method was photometric, and they constructed their standard curve for the photometer by adding known amounts of laevulose to filtrates from normal fasting blood. In this way they excluded interference by the colour obtained from blood in the fasting state, and their total blood-laevulose figures after the dose of laevulose represent rises above the initial level. They found higher figures

than Scott's, both for normal subjects and patients with liver disease, and they also noted that the peak of the laevulose curve often occurs earlier than one hour after the dose of laevulose. Their results in eight normal subjects were as follows: blood-laevulose before the dose of laevulose, zero; half an hour after, 8.5 to 18 mg. to 100 c.c.; one hour after, 10 to 16 mg. per 100 c.c.; two hours after, 3 to 8 mg. per 100 c.c. In most, but not all, of their cases of liver disease, there was an abnormally high peak, and in two cases in their series an abnormality was detected at the half-hour point which would have been missed if this point had been omitted.

In the present work we have followed Scott's practice of estimating blood-laevulose at hourly intervals. In view of the work of Stewart, Scarborough, and Davidson, the omission of the half-hour point is unfortunate, and some abnormalities may have been missed as a result of this. In each of the three studies, a different normal standard has been adopted, and this may be due partly to differences in technique. At present, pathological results must be interpreted in relation to normal standards obtained by the same method.

In assessing the clinical value of the test, it is necessary to consider not only the general association between deficient tolerance and damage to the hepatic parenchyma, but also the results which may be found in individual cases. It has been found that in chronic diseases of the liver, such as cirrhosis and carcinoma, the clinical signs and symptoms usually precede the appearance of deficient laevulose tolerance. This is to be expected; the liver certainly has a considerable functional reserve, and deficient function is not likely to be manifest until considerable disorganization has occurred. The estimation of laevulose tolerance cannot be used as a test for the existence of hepatic disease, but rather as an indication of the extent of liver involvement. As regards prognosis, the test does not necessarily give reliable guidance; for example, in cirrhosis of the liver there is the possibility of considerable regeneration of hepatic tissue, and the finding of deficient function at a particular time does not necessarily mean that the condition of the liver will deteriorate. Moreover, in cirrhosis, the severity of the symptoms depends mainly on the degree of fibrosis and portal obstruction, and this may not run parallel with the degree of damage to the hepatic parenchyma. These factors may explain the lack of correspondence between clinical severity and laevulose tolerance which is evident in some of our cases. It is probable, however, that curves including the half-hour point would have shown abnormalities in some of the cases in which we have failed to find them. As regards the differentiation between jaundice due to mechanical obstruction and jaundice due to toxic or infective hepatitis, it seems unlikely that the laevulose tolerance will be a reliable guide, since damage to the liver may occur as an effect of obstruction. Case 42 of the present series illustrates this difficulty. In the first attack of jaundice, the patient was thought to have toxic hepatitis; two years later he was found to have chronic pancreatitis with obstructive jaundice. He showed

deficient laevulose tolerance during his attacks of jaundice, and a normal curve in the interval between attacks.

Provided that its limitations are borne in mind, the laevulose tolerance test certainly has a place as an aid to diagnosis. It may be of use when some condition associated with liver damage enters into the differential diagnosis, as for example in distinguishing between haematemesis due to cirrhosis and haematemesis from other causes, or in distinguishing between haemochromatosis and other conditions associated with pigmentation of the skin. In splenic anaemia it may in some cases give warning of the onset of hepatic cirrhosis in advance of definite clinical evidence, but in such cases the deficiency in tolerance is likely to be slight, and repeated tests are desirable in order to avoid errors. It must be remembered that the finding of a normal laevulose tolerance does not exclude the possibility of liver disease.

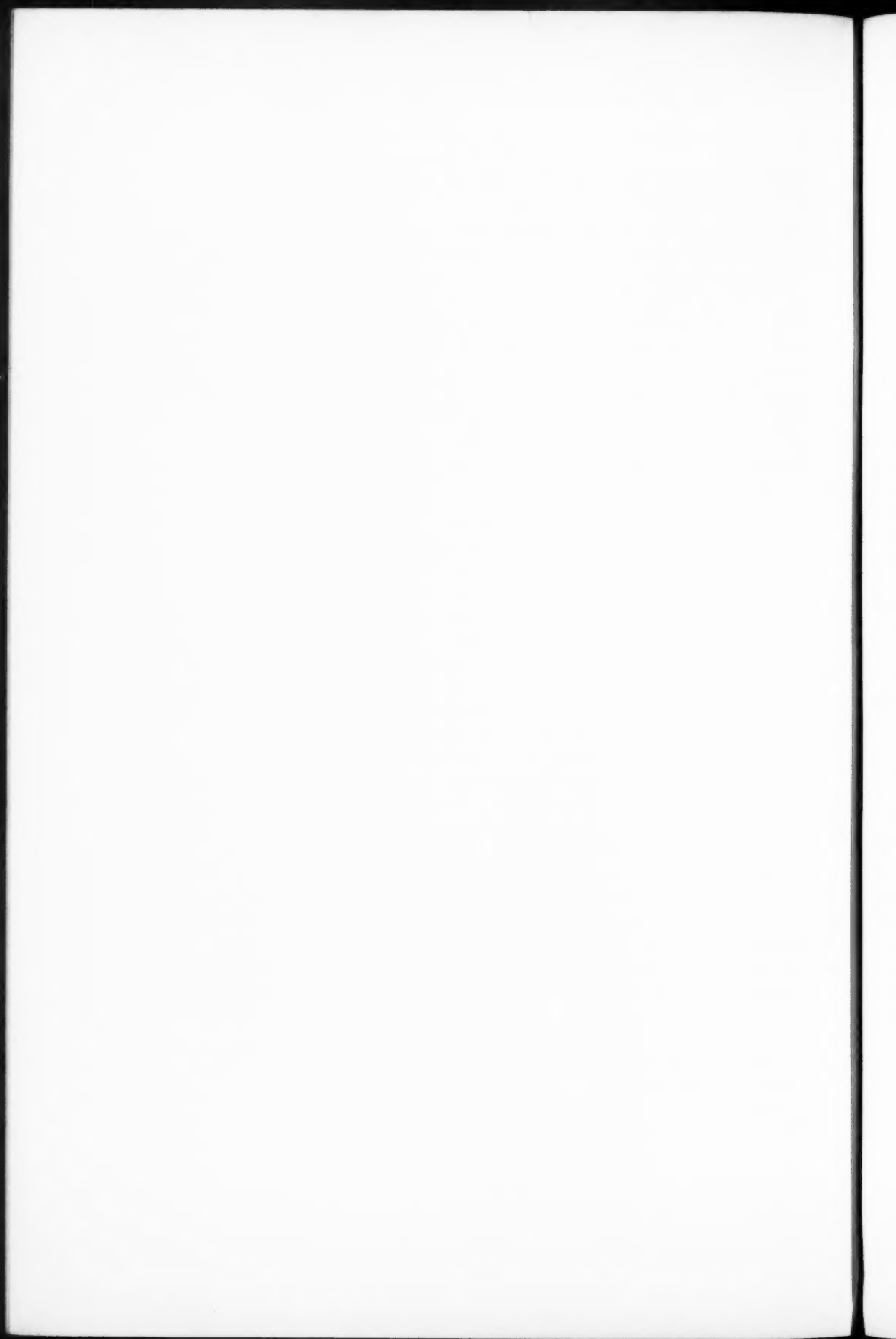
#### *Summary*

1. Estimations of the blood-laevulose by Patterson's method have been applied to the laevulose tolerance test for hepatic function.
2. The estimation of blood-laevulose is preferable to the estimation of total blood-sugar. When total blood-sugar is estimated variations in the blood-glucose mask the changes in blood-laevulose.
3. In general, there is a very definite association between deficient laevulose tolerance and damage to the hepatic parenchyma. The majority of cases of liver disease show abnormal curves.
4. In pancreatic diabetes the administration of laevulose causes a rise in blood-glucose, but the blood-laevulose curve is normal, provided the liver is normal. It is possible to study hepatic function in a diabetic subject by the use of blood-laevulose analyses, as is shown by the results in two cases of diabetes associated with liver disease.
5. In chronic diseases of the liver the appearance of clinical signs and symptoms usually precedes the development of deficient laevulose tolerance. Occasionally, however, it may be possible to demonstrate deficient hepatic function at a time when the clinical evidence is inconclusive.
6. In one case of von Gierke's disease the administration of laevulose caused no abnormal rise in blood-laevulose, although it did cause a rise in blood-glucose. The rise in total sugar was of the same order as that caused by the administration of glucose.

We wish to express our thanks to the Honorary Physicians and Surgeons of the Royal Victoria Infirmary for giving us the opportunity to make observations on their patients. We are indebted also to Dr. J. G. Thomson and Dr. B. Lennox for the use of their post-mortem findings, and to Dr. J. A. McKeon for his help in following some of the case histories.

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## PULMONARY TUBERCULOSIS COMPLICATING DIABETES MELLITUS<sup>1</sup>

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With Plates 24 to 26

THE frequent association of pulmonary tuberculosis with diabetes mellitus is an accepted observation of clinical medicine and the bad prognosis in such cases has been generally conceded. Before the introduction of insulin, pulmonary tuberculosis was probably the commonest cause of death in those diabetics who did not speedily die as a result of the diabetes itself. In the latter part of the nineteenth century Griesinger (1859) found tuberculosis in 42 per cent. of 250 fatal cases of diabetes; Windle (1883) reported its presence in 50 per cent. of the autopsies made on 333 diabetics; and as late as 1906 Naunyn found the two diseases associated in 41 per cent. of cases at post-mortem examination. After this date the autopsy records of diabetes show a decreasing percentage of cases in which active pulmonary tuberculosis was found. Montgomery reported 24 per cent. in 1912, Fitz and Murphy 19 per cent. in 1924, and Page and Henke 15 per cent. in 1932. From a consideration of these data, Root in 1934 came to the conclusion that the case for the abnormally frequent association of pulmonary tuberculosis and diabetes mellitus was established, and stated that tuberculosis is about two or three times as frequent at autopsy in diabetics as in non-diabetic cases. In considering these figures it must be remembered that they refer only to the finding of the two diseases together and throw no light upon which disease was responsible for death in the particular diabetic. Information on this point is provided by figures, from Joslin's clinic, given by Root (1937). From 1898 to 1914 pulmonary tuberculosis accounted for 4.7 per cent. of deaths; from 1914 to 1922 for 5.7 per cent. of deaths; and from 1922 to 1935 for 6.6 per cent. of deaths. It will be seen from these figures that despite the improvement in the treatment of diabetes, consequent upon the use of insulin, and despite the fall in the death-rate from pulmonary tuberculosis in the general population, the death-rate amongst diabetics from pulmonary tuberculosis is not diminishing, but on the contrary is actually increasing.

It is a general clinical impression that pulmonary tuberculosis in the diabetic usually appears suddenly and progresses rapidly so that at the time of its recognition the lung disease is so advanced as often to render the prognosis hopeless. Such a sudden appearance of pulmonary tuberculosis may occur for one of two reasons. Either the diabetic is unusually liable to

<sup>1</sup> Received January 18, 1938.

fulminant pulmonary tuberculosis, or the tuberculosis commences deep in the lung and remains undetected until it has spread to the surface and gives rise to clinical signs. If the former of the two alternatives is correct, then we cannot hope to do much to reduce the mortality from pulmonary tuberculosis in diabetics other than by preventing the patient's exposure to such infection;

TABLE I

*Incidence of Clinically Detectable Pulmonary Tuberculosis in Cases of Diabetes Mellitus*

Author.	Year.	Total number of diabetics.	Number of diabetics with pulmonary tuberculosis.	Incidence of pulmonary tuberculosis %
Sosman and Steidl	1927	1,074	32	3.0
Rosenberg and Wolf	1927	1,000	40	4.0
Joslin	1928	3,000	43	1.4
Adams	1929	1,000	10	1.0
Lorenzen	1929	851	50	5.5
Escudero	1929	476	22	4.5
Fitz	1930	1,529	35	2.3
Murphy	1931	827	40	4.8
Wendt and Peck	1931	1,073	42	4.0
Kennedy	1933	2,500	41	1.6
Total		13,330	355	2.7

if the latter be true, then earlier diagnosis of the pulmonary lesion offers hope of more successful treatment. It is, therefore, of considerable importance to know which of these two alternatives is correct, and to this end information is required on several points. We must know firstly the incidence rate of pulmonary tuberculosis in diabetics when the diagnosis is made by clinical means and when radiology is used only to confirm or refute a clinical opinion; secondly, the incidence rate when every new case of diabetes is examined radiologically as a routine; thirdly, the incidence rate in efficiently treated patients in whom radiological examination has excluded the presence of tuberculosis when these patients first came under treatment; and fourthly, the course of pulmonary tuberculosis in treated diabetics. Sufficient evidence is now available to form a general impression as to the incidence of clinically detectable tuberculosis in diabetics. Figures from recent papers are given in Table I. The incidence rate in different clinics varies considerably, but to some extent this can be explained. The higher rates are on the whole reported from those diabetic clinics whose patients come from an urban and often poor population. The figures given in Table I can be regarded only as of general significance, for they refer not only to pulmonary tuberculosis discovered when the patient first attends for treatment of his diabetes, but include also those cases who later developed pulmonary lesions.

There is little evidence as to the incidence of pulmonary tuberculosis amongst series of diabetic cases who were examined radiologically, as a routine, on their first attendance. Kennedy (1933) reports an incidence of 1.6 per cent.; Sosman and Steidl (1927) 17 cases amongst 182 diabetics, an incidence of 9 per cent. The latter report is of especial value, for it is there recorded

that in the same hospital the incidence rate of tuberculosis amongst 1074 diabetics, as diagnosed clinically, was 3 per cent. This discrepancy between radiological and clinical diagnosis suggests that those diabetics who develop clinical pulmonary tuberculosis whilst under treatment may have been suffering when first seen from active tuberculosis, which would have been, even then, radiologically evident. It is obviously of great importance to learn if a discrepancy fraught with such significance exists, and the results recorded in this paper are in part presented with this object. Root (1934) has published figures showing the incidence of tuberculosis in groups of diabetics who have suffered from diabetes for varying periods. By radiological examination he found definite or suspected pulmonary tuberculosis in 6.8 per cent. of patients in whom diabetes had been present for one to four years, and in 6.0 per cent. of those who had had diabetes for five to nine years. But as far as I am aware there are no figures available at present showing the subsequent incidence of pulmonary tuberculosis amongst diabetics in whom this disease had been excluded by radiological examination at the patient's first attendance.

The evidence in the present paper is given in two sections. The first deals with the diagnosis and association of pulmonary tuberculosis and diabetes mellitus. In this the findings on routine clinical and routine X-ray examination of the chest will be compared, an attempt will be made to clarify the radiological signs of early pulmonary tuberculosis in diabetics, and factors influencing the association of the two diseases will be discussed. In the second section the results of treatment and the rationale of the therapeutic methods used will be considered.

#### I. *Diagnosis and Association of Pulmonary Tuberculosis and Diabetes Mellitus*

*Diagnosis.* Two hundred and thirty consecutive cases of proved diabetes mellitus attending the Medical Unit Diabetic Clinic at University College Hospital, London, between July 1st 1935 and November 1st 1937 were each examined clinically by myself and each had an X-ray of the chest taken. Two cases who came up in this time interval are excluded from this series because they were referred to the clinic from sanatoria where they had already received treatment for pulmonary tuberculosis. The patients were of the hospital class and the distribution curves for age and for sex at the onset of diabetic symptoms of this series were the same as for a previous series of 400 cases who attended before July 1935. These distribution curves for the two series agree closely, both as regards the total number of cases commencing in each decade and as regards the sex distribution, with similar curves published by Joslin (1937) for a series of 6,357 diabetics. The present series of 230 cases may, therefore, be regarded as a representative sample. In this series, 15 cases (6.5 per cent.) showing radiological signs suspicious or diagnostic of pulmonary tuberculosis were found at the time of the patient's first attendance. The particulars of these patients are given in Table II. Of

these 15 cases, eight (3.5 per cent.) had radiologically undoubted lesions of pulmonary tuberculosis, the remaining seven cases (3.0 per cent.) showed radiological appearances which were regarded as probably due to tuberculosis.

The majority of patients attending this diabetic clinic have received no previous treatment, but have been sent up by their general practitioner within a few days of diagnosis. Of the 15 cases showing signs of pulmonary tuberculosis, nine had been untreated. The remaining six had received some treatment, but this was in every case so inadequate as to be negligible. For practical purposes these 15 cases can be considered as untreated diabetics, and this view is supported by the finding that the length of time between the onset of the symptoms of diabetes mellitus and the detection of the pulmonary lesion was of similar duration in both the six 'treated' and nine untreated patients. The average interval for all 15 cases was 16.7 months, for the 'treated' cases 19 months, for the untreated cases 15.1 months. In each of the 15 cases diabetes mellitus appeared to have preceded the pulmonary lesion. This statement is made not only because in each case diabetes mellitus was detected first, but also because the radiological appearance of the pulmonary lesions was that of recent infection. The average age of the 15 patients was 38.1 years (standard deviation 14.4), and in the group there were five females and 10 males. A history of contact with tuberculosis could be elicited in only two cases.

*Clinical Features.* Two cases out of the 15 were suffering from tuberculous broncho-pneumonia. For convenience of discussion these will be dealt with first. In neither did the clinical examination leave any doubt as to the diagnosis, and the radiological findings and the detection of tubercle bacilli in the sputum served but to confirm the clinical decision. In the 13 other cases neither on the basis of symptoms nor signs could even a tentative diagnosis of pulmonary tuberculosis have been made, and in only two of the cases were there any clinical grounds for suspicion of its presence. Point is lent to this statement by the fact that this series of 230 cases of diabetes mellitus was collected with the object of determining the incidence rate of tuberculosis in diabetics living in London, and each case was examined with this object in mind. The evidence for regarding the radiological findings as indicating pulmonary tuberculosis will be discussed in detail later. An analysis of the symptoms and signs in these 13 cases emphasises the slowness of the clinical manifestations. In 11 cases cough was denied. Loss of weight was reported by all, but as untreated diabetes itself produces this symptom, it is of little moment. No case gave a history of night sweats. Sputum was usually absent. This latter finding is remarkable. Cases in which the X-ray revealed cavities in the lung produced no sputum at all.

Physical signs were found in only two of the 13 cases. In one case diminished movement was found on the side of the lesion; in the other, one week after X-rays had revealed an extensive pneumonic condition with cavities extending from the right hilum, a few fine râles were heard at the back at the level of the lesion in the lung. In three cases fever rising up to 99.5° F. was found on

admission to hospital, but in each case it subsided to normal in a week. The pulse-rate remained elevated for a longer time, and in one case took eight weeks to return to normal even though the patient was at rest in bed. It would appear that some of these cases may be febrile whilst ambulant, but afebrile whilst at rest. In any case, fever and elevation of the pulse-rate of this degree are not such as to attract attention unless the patient is under close observation. Tubercle bacilli were found in the sputum of only one of the 13 patients, and in this case on only one occasion. Negative results were obtained on all other sputa. It should be noted in this connexion, however, that sputum was absent in the majority of cases and minimal in the rest, so that little opportunity was afforded for its examination. The blood counts in these cases were essentially normal. The sedimentation rate, measured at one hour in a column of blood 10 cm. long in a tube of 2 mm. bore, was usually, but not always, raised to the region of 20 or 30 mm. in cases in which the radiological evidence indicated tuberculosis. In one case which progressed whilst under treatment from an early suspicious radiological finding to definite pulmonary tuberculosis, the rate rose from an initial figure of 6 mm. to 40 mm. In the patients with early lesions the rate was normal.

It thus appears that in the diabetic with early pulmonary tuberculosis the ordinary symptoms of the disease are not manifest, the ordinary physical signs in the chest are absent, and the usual pathological investigations yield negative results. The conclusion is that the only sure way to detect the disease in diabetics is by routine radiological examination of the chest of every patient. This conclusion will not be weakened by my drawing attention to two clinical points which should raise a suspicion that a particular diabetic has pulmonary tuberculosis. When a previously untreated diabetic is given energetic and adequate treatment for his diabetes he becomes aware very rapidly of an improvement in his subjective sense of well-being, although, judged by chemical tests, his disease may yet be far from being perfectly controlled. This is so usual that if this subjective improvement fails to occur, and the patient denies any access of strength, the suspicion should at once enter the mind that some source of toxæmia is present. Such patients by contrast with other diabetics can often be suspected at sight. The uncomplicated diabetic, after a week's vigorous treatment, looks alert and hopeful; the diabetic with a pulmonary lesion looks pale, despondent, and weary.

The second point is the association of pulmonary tuberculosis in diabetics with true diabetic cataract. In diabetics two main types of cataract occur. One is common; this is the ordinary senile cataract which takes years to impair vision and more years to mature. The other is rare, and characteristic of diabetics. It occurs more commonly in the young, and causes blindness in a matter of days, weeks, or at most months. An unusually large number of patients are referred to this diabetic clinic from hospitals for diseases of the eye, and during the last seven years 10 cases of this rare cataract have been seen. Four had pulmonary tuberculosis. Root (1934) mentions two cases, and White (1932) one case, in which this type of cataract was found in

association with pulmonary tuberculosis. The association is capable of simple explanation. True diabetic cataract occurs only in severe and neglected cases of diabetes; pulmonary tuberculosis is especially liable to attack such cases. The detection of this type of cataract necessitates a radiological examination of the chest.

*Radiological appearances.* From the foregoing considerations it is clear that the only hope of diagnosing the pulmonary lesion in diabetic patients at an early stage, when it is susceptible to treatment, lies in its recognition in the radiogram. Each case in this series of 230 diabetics has had a radiogram of the chest taken and has been directly viewed under the X-ray screen. In no case has the screening examination shown a lesion that was not evident in the radiogram, and in three of the 13 cases with pulmonary lesions the suspicious appearance was visible only in the radiogram. For descriptive purposes in this paper the appearance in the radiogram only will be considered. The difficulty of demonstrating the characteristic features of these early radiological appearances arises from two sources. Firstly, the scanty clinical data provided by these cases do not in themselves establish the diagnosis of pulmonary tuberculosis; and secondly, as the majority of the cases improve or heal under treatment the progress of the case adds no further evidence as to the nature of the lesion. The significance of the small pulmonary lesion can, therefore, only be inferred. For this reason we shall first consider the radiological appearances in the chest of an established case of clinical pulmonary tuberculosis which were discovered before routine X-ray of the diabetic's chest was practised and then show that appearances indistinguishable from these were found in the lungs of the 13 diabetics in whom there was no definite clinical evidence of tuberculosis. The proved case of pulmonary tuberculosis was a female (A.V.), aged 51, who was admitted with diabetes in February 1933. Tubercle bacilli were found in the sputum and clinical examination of the chest revealed a cavity at the right apex. An X-ray confirmed this finding and showed also extensive homogeneous infiltration in the upper half of the right lung (Plate 24, Fig. 1 a). The left lung was free of disease. After eight months treatment the X-rays (Plate 24, Fig. 1 b) failed to reveal the cavity, the infiltration had disappeared and all that remained to be seen was an accentuated interlobar fissure and a faint patch of mottling in the second interspace<sup>2</sup> nearer the periphery than the mediastinum. The next X-ray taken in April 1934 (Plate 24, Fig. 1 c) showed that this mottled patch had spread and changed to form a smooth infiltration involving the lateral half of the lung in the first and second interspace. By September 1934 this infiltration had condensed to a homogeneous circular shadow in the lateral half of the second interspace and, thereafter the process of condensation continued (Plate 24, Fig. 1 d) until in November 1937, the patch was seen to be disappearing in disintegration. Plate 24, Figs. 1 c and 1 d should be compared with Plate 25, Figs. 2 a and 2 b.

<sup>2</sup> Descriptive orientation of lesions in the lung refers to the anterior ends of the ribs as they appear in the X-ray.

The X-rays shown in Plate 25, Figs. 2 *a* and 2 *b*, were obtained from patient No. 8 of the routine X-ray series (Table II), a woman aged 61 admitted with a history of symptoms of diabetes mellitus for 9 months. The pulse and temperature were normal, the sputum showed no tubercle bacilli, and there were no abnormal physical signs in the chest. X-rays (Plate 25, Fig. 2 *a*)

TABLE II

*Particulars of 15 Diabetics in whom Pulmonary Tuberculosis was Discovered by the Routine X-ray of 230 Diabetics on their First Attendances between July 1935 and October 1937*

	Sex.	Age.	Duration of diabetes mellitus in months.	'Treated' (T) or 'Untreated' (U).	Clinical examination.	Radiological appearance.	Initial stabilizing insulin requirement.	Special treatment for Tb.	Last radiological appearance before Nov. 1937.
1	M	21	12	U	Negative	Hilar pneumonic	60	A.P.	A.P.
2	M	15	24	T	Negative	Hilar pneumonic	75	A.P.	A.P.
3	F	61	6	U	Negative	Early mottled infiltration	20	None	Scar
4	M	23	12	T	Negative	Early pneumonic infiltration	60	None	Disappeared
5	M	29	36	T	Negative	Subapical pneumonic	60	None	Disappeared
6	F	44	60	U	Suspicious	Early mottled infiltration	20	A.P.	A.P.
7	M	50	12	U	Negative	Early mottled infiltration	54	None	Scar
8	F	61	9	U	Negative	Early mottled infiltration	30	None	Small focus
9	M	35	12	U	Negative	Early mottled infiltration	25	None	Faint mottling
10	F	40	24	U	Negative	Hilar pneumonic	55	None	Disappeared
11	M	21	8	T	Negative	Early pneumonic infiltration	10	None	Smaller dense foci
12	M	43	24	T	Positive	Bilateral broncho-pneumonia	(100+)	None	(Dead)
13	M	28	10	T	Negative	Early pneumonic infiltration	75	None	Disappeared
14	M	50	3	U	Positive	Bilateral broncho-pneumonia	(80+)	None	(Dead)
15	F	51	9	U	Negative	Early mottled infiltration	30	None	Scar

revealed on the right side an ill-defined ovoid patch, 3.5 × 3 cm., of confluent mottling in the lateral third of the lung and centred on the upper edge of the third rib. The patient was difficult to balance even with insulin and felt little benefit from the control of her diabetes. The radiological appearance two months later was unchanged. After six months' treatment, however, the patient's subjective sense of health returned and an X-ray taken nine months later showed that the diffuse mottling had condensed into a circular more uniform patch 1.5 cm. in diameter (Plate 25, Fig. 2 *b*). Thereafter the condensation continued and at present (November 1937) is even smaller and better defined, and the patient is feeling perfectly well. Since the patient felt the first improvement in health she has gained 22 lb. in weight, the treatment having been the same since the discovery of the disease. It will

be seen that the X-ray appearances in this case are almost identical with those of the previous case in which tuberculosis had been proved to be present (cf. Plate 24, Figs. 1 *c* and 1 *d*).

Patient No. 5 (Table II) was a man aged 29 who had been treated for diabetes for three years. He came up for treatment in August 1936. For the previous two years he had neglected his diet and had not attended hospital, so that he had continued to take the initial small dose of insulin although he obviously now required much more. The patient felt weak and listless, but there was no clinical evidence of tuberculosis. The sedimentation rate was 33 mm. in 1 hour. Routine X-ray examination (Plate 25, Fig. 3 *a*) revealed beneath the inner end of the right clavicle an area,  $4 \times 2.5$  cm., ovoid in shape and from the edge of which wisps of infiltration spread into the adjoining lung tissue. The texture of the lesion, which is shown in detail in Plate 25, Fig. 3 *b*, was uniform, and on comparison it will be seen to be similar to that of the lesions shown in Plate 24, Figs. 1 *a*, 1 *c*, and Plate 26, Fig. 4 *b*. The diabetes was controlled with some difficulty, but two months later the patient began to feel better and commenced to put on weight. An X-ray taken at this time showed that the wisps of infiltration had disappeared and the area was a little smaller. In December 1936 the area was much smaller, and a further X-ray in April 1937 (Plate 25, Fig. 3 *b*) showed that the lesion had practically disappeared. At this time the patient felt extremely well and had gained 26 lb. since treatment commenced.

The next patient, No. 10 of the routine series (Table II), was a woman aged 40 who had had untreated diabetes for two years and during this time had been nursing her husband who was suffering from pulmonary tuberculosis. On admission a temperature of  $100^{\circ}$  F., a pulse-rate averaging 100, and sedimentation rate of 10 mm. in 1 hour were found. Apart from these findings there was no evidence, either clinical or pathological, of the presence of tuberculosis, but the X-rays revealed a smooth infiltration spreading from the left hilum, a cavity in the middle of this (Plate 26, Figs. 4 *a*, 4 *b*), and a faint mottling round a calcified patch in the third right interspace. The patient's diabetes was rapidly controlled and radiograms taken at monthly intervals. At the end of the first month the mottling in the third right interspace had disappeared and the lesion in the left lung was shrinking back on the hilum. At the end of the second month the lesion at the left hilum was smaller and no longer uniform in texture, but reticulate. At the end of the third month (Plate 26, Fig. 4 *c*) no lesion was visible. In the three months that the patient was in hospital she gained 20 lb. in weight, and nine months later she had gained a further 33 lb. and showed no clinical or radiological evidence of tuberculosis.

This type of lesion—a wedge of infiltration, with cavities, extending from the hilum towards the periphery—is the most characteristic type of pulmonary tuberculosis in diabetics. It has been described by Kennedy (1933), Sosman and Stiedl (1927), and Dorendorf (1928). It was present in four of the 15 cases discovered by routine X-ray, and in none of these were tubercle bacilli

demonstrated in the sputum. But in two cases of this type discovered in an earlier series we were able to detect the bacilli.

Patient No. 4 (Table II) was a man aged 23 who had had diabetes for one year. No evidence of tuberculosis was found and the patient said that he did not feel ill, apart from the symptoms of diabetes. The X-ray (Plate 26, Fig. 5) revealed a small pear-shaped homogeneous area in the lateral portion of the first left interspace. Three months later only the inner end of the pear-shaped area could be seen, and seven months later this had disappeared.

The evidence for regarding these early radiological lesions as tuberculous in nature must now be considered. Firstly, the sequences of radiograms in this series prove that the lesions are chronic. The radiological appearances cannot be attributed to such a condition as a small area of collapse resulting from the obstruction of a bronchus by mucus. The duration of the lesions for months or years, the slow changes in the extent and texture of their radiological appearance, and the fact that they either disappear slowly or give place to scar tissue, all point to a chronic inflammation of the lung tissue.

Secondly, the lesions are identical in appearance with those whose origin and progress have been watched in the previously unaffected portions of the lungs in cases of proved pulmonary tuberculosis in diabetes. In one proved case of pulmonary tuberculosis from a previous series, extensive tuberculosis of one lung and an early lesion of the other, such as we have described, were seen in the radiogram shortly before death. At autopsy the tuberculous nature of the early lesion was proved.

Thirdly, cases with such early lesions may progress to fully developed pulmonary tuberculosis. In one case of this series (Case 2) a typical early lesion progressed until it formed a wedge-shaped mass of infiltration spreading out from the hilum and containing a cavity at its apex. Tubercle bacilli were not demonstrated in the sputum from this particular case, but they have been demonstrated in other cases with a similar radiological appearance. Another case (E. D.), not of this series, developed clinical and radiological signs of tuberculosis, and tubercle bacilli were demonstrated in his sputum, after he had been under treatment for diabetes mellitus for 18 months. On searching the records, an X-ray was discovered which had been taken when the patient first attended for treatment of his diabetic condition and this showed a typical early lesion which had been overlooked at the time.

Fourthly, in all save the earlier cases the clinical condition of the patient can be correlated with the change in the radiological appearance in the chest. If the lesion regresses, the patient's subjective sense of health improves, his energy returns, his weight increases, his sedimentation rate falls, and the diabetes becomes easier to control. If the lesion progresses the reverse tends to happen.

These considerations can be summarized by saying that the radiological appearances are those of a chronic inflammatory lesion, they are identical in appearance with new lesions appearing in the lungs of proved cases of

pulmonary tuberculosis, they can progress until they are radiologically, and the cases clinically, typical of pulmonary tuberculosis, they are quantitatively correlated with clinical evidence of toxaemia. In the light of this evidence it appears permissible to conclude that the radiological lesions described are those of early pulmonary tuberculosis as seen in diabetes.

*Discussion on diagnosis.* Pulmonary tuberculosis in the diabetic has long been stated to be characterized clinically by a fulminant onset. In recent years, however, radiological examination has revealed that widespread involvement of the lung may be present long before clinical signs become conspicuous. This infrequency of clinical signs has been noted by Fishberg (1932), Dorendorf (1928), Kennedy (1933), and Sosman and Steidl (1927), but denied by Wassmund (1927), Curschmann (1928), Fitz (1930), and Myers and McKean (1935). It is highly probable that this divergence of opinion can be explained by those who deny the statement being concerned with sanatorium experience, and therefore presumably with fully developed cases of pulmonary tuberculosis, whilst those who support the statement are those engaged in the clinical practice of large hospitals and who are thereby brought in contact with early cases of the disease. The same divergence of opinion is manifest with regard to the frequency with which the tubercle bacillus can be demonstrated in the sputum, physicians at sanatoria claiming that it can be demonstrated in practically every case, whilst physicians in diabetic clinics are impressed by its absence. In my experience both physical signs and symptoms of pulmonary tuberculosis have been detectable in all cases in which the tubercle bacillus has been present in the sputum, but they have been inconspicuous in cases in which it could not be found after repeated examinations.

The infrequency of physical signs in early cases and the apparently fulminant onset of clinical pulmonary tuberculosis in the diabetic can both be explained by the deep-seated situation and nature of the early lesions in the lung. Many of the lesions are perihilar and those which are situated farther out in the lung substance tend to spread more rapidly towards the hilum than to the periphery. As a result, when the disease becomes sufficiently superficial to give physical signs the segment of the lung deep to it is already extensively involved. The silent nature of the infiltration is also facilitated by the types of lesion. The type of tuberculosis seen in diabetics is usually pneumonic, with little or no fibrosis—a type unassociated with obvious physical signs—and although it tends to early cavitation, the smallness of the cavities and the minimal amounts of sputum do not provide the conditions necessary for the clinical signs of cavitation. This pneumonic spread from the hilum has been noted so frequently in diabetes that Sosman and Steidl (1927) have designated it 'diabetic tuberculosis'. It was present in 21 out of their 29 cases, four of our 15 cases, and 16 of Kennedy's (1933) 41 cases. It appears, therefore, that the apparently fulminant onset of clinical pulmonary tuberculosis in the diabetic is to be attributed, as Dorendorf (1928) suggested, not to a peculiarity on the part of the diabetic, but

rather to the type and to the deep-seated situation of the pulmonary disease in its early stages.

From these considerations it is apparent that the only hope of diagnosing pulmonary tuberculosis at an early stage in diabetic patients lies in the routine and periodic X-ray examination of all cases. The gloomy prognosis in diabetics with pulmonary tuberculosis sufficiently advanced to give clinical signs of the disease and the excellent results of treatment in those in which the disease has been detected at an early stage render such routine examination imperative.

Before leaving the question of the radiological appearance of early tuberculosis, attention may be drawn to one point. The small circumscribed homogeneous lesion is claimed by Assman (1934) to denote commencing tuberculosis. In three of our cases this focus has developed whilst they were under observation, and in each case it occurred, not as a primary lesion, but as a condensation of an earlier more diffuse mottled lesion, and this condensation continued to shrink until it eventually disappeared or was replaced by scar tissue. It would appear that the Assman focus should be regarded, not as evidence of commencing tuberculosis, but as a sign of healing tuberculosis.

#### *The Association of Diabetes and Pulmonary Tuberculosis*

In recent years the statement that pulmonary tuberculosis is an unusually frequent complication in patients with diabetes mellitus has been challenged (see Fishberg, 1932). Knowledge is required on two points: is the untreated diabetic unusually liable to pulmonary tuberculosis; is the treated diabetic, despite the control of his diabetes, also unusually liable to this complication? Evidence in support of the view that untreated diabetes predisposes to pulmonary tuberculosis is provided by observations as to the incidence of diabetes amongst patients with tuberculosis, and of tuberculosis amongst patients with diabetes. Most physicians are agreed that in the great majority of cases the diabetes mellitus precedes the pulmonary tuberculosis (Fishberg, 1932). The data from the present series of cases favours this opinion. In 29 diabetics with pulmonary tuberculosis seen at this clinic the symptoms of diabetes preceded the discovery of the pulmonary tuberculosis in 26 cases, the tuberculosis came first in two, and in one case the history was equivocal. Further evidence indicating diabetes mellitus as predisposing to pulmonary tuberculosis is derived from a consideration of the age at which the diabetic develops this complication. The maximum incidence of pulmonary tuberculosis in non-diabetics is greatest in young adults; in diabetics it is greatest in middle life when diabetes is most common. In this present series the age at which the pulmonary lesion appeared averaged thirty-eight years, in Joslin's (1928) series it was forty-five years, and Banyai's (1931) forty-two years.

Out of the 230 cases who were examined radiologically on their first appearance at the clinic, pulmonary tuberculosis was found in 15. All these

15 cases were either actually or virtually untreated. In eight of the 15 cases the radiological findings were so pronounced that it is unlikely that any radiologist would have failed to suggest that pulmonary tuberculosis was present. Thus by any standards 3.5 per cent. of the present series of diabetics would have been diagnosed as having pulmonary tuberculosis before adequate treatment of the diabetes was commenced, and by the standards we have come to accept 6.5 per cent. were so diagnosed. That an unusually high incidence is indicated by these figures is clear; and the further facts that these cases had on the average symptoms of diabetes mellitus for only 16.7 months before they came up for treatment, and that no further cases have since been detected in this same group of 230 diabetics, suggests that the traditional view that *untreated* diabetes mellitus predisposes to pulmonary tuberculosis is correct. Further support of this view is found in the high incidence or rapid progress of tuberculosis in those patients who have refused to co-operate in the treatment of their diabetes. The degree to which treatment has been disregarded is difficult to assess, but definite evidence of imperfect control of some is provided by the development of true diabetic cataract. In three cases, not of the present series, such a cataract developed. These patients attended the clinic two or three times after their first visit, then disappeared and were not seen again until one to four years later. All had bilateral cataracts, and in addition two had pulmonary tuberculosis.

In cases in which pulmonary tuberculosis was present and the diabetic treatment was either inadequate or disregarded, the pulmonary disease invariably progressed; in similar cases who adhered to treatment the disease was usually arrested, and in some cases apparently cured. Finally, pulmonary tuberculosis is a complication of severe rather than mild diabetes. All the cases seen at the clinic have been sufficiently severe to require insulin. In the light of the evidence now available it appears to be beyond reasonable doubt that untreated diabetes predisposes to the development of pulmonary tuberculosis.

The question as to whether diabetics are unusually liable to pulmonary tuberculosis, even though their diabetes is controlled, is as yet undecided. Root (1934) carried out X-ray examinations of the chests of groups of diabetics who had been under treatment for varying lengths of time. In each group there was a high incidence of tuberculosis. It should be noted, however, that these patients had not all had an X-ray of the chest at their first examination and the question arises as to whether the pulmonary tuberculosis, which was discovered in the subsequent years of treatment, was acquired after treatment was instituted, or had been present at the first attendance, and its progress so retarded by the subsequent treatment that it only became manifest later. The case E. D. previously cited may be quoted in this connexion. Originally treated for diabetes in December 1930, tuberculosis was not discovered until May 1932. In this interval he had been working and had not received the special treatment for diabetes with pulmonary tuberculosis. Search then revealed a radiogram taken in

December 1930 and this showed definite early pulmonary tuberculosis. Clinical experience of the rapid extension of such early lesions in untreated diabetics suggests that in this case the moderate control of the diabetes which was established had been sufficient to retard the progress of the tuberculosis.

In this diabetic clinic no evidence has appeared of a high incidence of pulmonary tuberculosis amongst treated diabetics. Owing to the fact that many patients return to their family physicians when the diabetes has been brought under control, complete figures cannot be produced. There are, however, over 300 diabetics now visiting the clinic regularly whose first attendance was between January 1931 and July 1935, that is before routine radiological examination of new cases was commenced. During the last two years radiograms of the chests of practically all these patients have been secured, and in only two cases has early pulmonary tuberculosis been found. This incidence rate of approximately 0.7 per cent. in treated diabetics strongly suggests that treated diabetic patients are no more liable to develop pulmonary tuberculosis than non-diabetic subjects, and, when contrasted with the incidence rate of 6.5 per cent. in untreated diabetics, it shows clearly the influence of uncontrolled diabetes in predisposing to tuberculosis. I would suggest that a high incidence of tuberculosis amongst treated diabetics indicates either that the diabetic treatment is inadequate or, if this is not so, that cases of pulmonary tuberculosis are escaping detection on their first attendance and only manifesting themselves subsequently.

## II. Treatment

*Results.* It might reasonably have been expected that the introduction of insulin into diabetic therapeutics would have sensibly affected the mortality rate in cases with pulmonary diseases, but the figures published by Root (1934) show that this has not been the case. The 160 patients reported by him survived on the average for three years after diagnosis of tuberculosis, and this result appears to accord with the general experience. Adams (1929) found that seven out of his 10 cases died within four years; Lorenzen (1929) that 96 out of his 116 patients died within three years; Wiener and Kavee (1936) that 20.8 per cent. of 218 cases died within one year, and a further 47.2 per cent. within two years; Wassmund (1927) that 20 per cent. of his 60 cases died within seventeen months of diagnosis; Fitz (1930) from an experience of 35 cases, that 63 per cent. died within one year, 83 per cent. in less than three years, and only 13 per cent. survived more than four years; Kennedy (1933) that the average duration of life in his series was 12.9 months, and that 16 out of 25 cases died within eight months. As an offset to this gloomy evidence, cases showing favourable prognosis are recorded. Root (1934) in his review reports several such, Wessler and Hennell (1933) report nine cases, whilst Myers and McKean (1935), out of a series of 80 cases seen between 1929 and 1934, report 16 arrested, six quiescent, eight improved, three untraced, 12

unimproved, and 35 dead. The last authors state that, in their opinion, diabetics with pulmonary tuberculosis react to treatment in a manner that compares favourably with that of non-diabetics with pulmonary disease of the same intensity. Nevertheless, favourable progress or recovery is so rare that it is still considered an occasion for a detailed case report (Shephardson and Noble, 1937; Lenoir and Scherrer, 1927; Blum, 1929).

The justification for publishing the present small group of 29 cases of associated pulmonary tuberculosis and diabetes mellitus is that the improvement with treatment has exceeded any hitherto reported. These 29 cases include the 15 patients who were discovered in the series of diabetics submitted to a routine radiological examination of the chest, and the remainder have attended the clinic at some time or other since January 1931. Six patients are dead; four died of acute tuberculous bronchopneumonia within four months of their first attendance. Of the other two fatal cases, one discharged herself from the clinic on being informed at first attendance that she had tuberculosis, disregarded all treatment, and was brought back, on the verge of diabetic coma, ten months later, having developed bilateral diabetic cataract and extensive pulmonary disease. She died five months later. The other case died four years after her first attendance when the diagnoses were made. Although she took insulin fairly regularly, she refused to continue with artificial pneumothorax treatment and to regulate either her life or her diet. The fact that after her first stay in hospital she was next seen when she returned in diabetic coma two months later, having in the meantime contracted gonorrhoea and syphilis whilst in pursuit of a livelihood as a prostitute, shows how little chance of adequate treatment was possible in this case.

The remaining 23 cases are alive. In seven of these there is now no clinical or radiological evidence of pulmonary tuberculosis. This apparent cure has, in different patients, taken from five months to four and a half years to complete. One further case shows marked fibrosis of the right upper lobe, but judging by her clinical condition, absence of tubercle bacilli in the sputum, normal sedimentation rate, and her persistent freedom from glycosuria during the last five years on 10 units of insulin daily, the pulmonary disease is at least arrested. Nine cases, judging by the steady improvement in clinical condition and radiological findings, are healing, but the longest period that any of these have been under observation is two years. One further case cannot be traced, but when last seen, fifteen months ago, one year after diagnosis, she was in excellent health. Of the remaining five cases, three are apparently quiescent, one is slowly deteriorating, and one, diagnosed eleven months ago, has within the last few weeks commenced to put on weight, become sugar-free, and begun to feel subjectively improved. It may be objected that these results appear unduly favourable because they include a large series of minimal lesions. If we exclude from these 23 cases the seven in which the pulmonary lesion was small, and consider only the 16 cases in which a definite diagnosis would

have been made either on clinical or on radiological findings, the results are as follows:—Apparently cured, five cases; arrested with fibrosis, one case; healing, four cases; untraced, one case; quiescent, three cases; deteriorating, one case; commencing improvement, one case. It is of interest to note that of the six of our cases showing the hilar pneumonic type of spread, three are apparently cured, two are healing, and the remaining one is now showing improvement. The time since diagnosis ranges from twenty-one months to seven months. The prognosis given by Kennedy (1933) for this type of 'diabetic tuberculosis' is an average of 9.3 months' survival.

*Treatment.* In the numerous reports on the results of treatment in cases of associated pulmonary tuberculosis and diabetes mellitus considerable attention is devoted to the methods used in the treatment of the tuberculosis, but little or no reference is made to the measures adopted against the diabetes. One is left with the impression that the particular form of diabetic treatment that a tuberculous diabetic receives is not determined by considerations of what is best for such cases, but simply by the particular treatment which is in local favour for uncomplicated cases of diabetes. Yet, since it has long been thought that diabetes predisposes to the development of tuberculosis, it is surprising that the primary importance of the diabetic treatment has not been recognized, and that investigations have not been directed towards determining what particular type of diabetic treatment is most efficacious. From my own experience I have no doubt at all that in these cases efficient treatment of the diabetes is of paramount importance, for the pulmonary tuberculosis in two-thirds of my cases has either recovered or improved with no further measures than control of the diabetes, and rest. Treatment will, therefore, be discussed in two sections; first of the diabetes, and second of the tuberculosis.

*Diet.* The diet which I have found satisfactory in the treatment of diabetes with pulmonary tuberculosis was constructed originally for another purpose. The high incidence of pulmonary tuberculosis in cases showing true diabetic cataracts has been mentioned previously. These cataracts, in untreated diabetics, invariably progress to cause blindness in a few weeks or months, and this progress cannot be arrested by controlling the diabetes on a low-carbohydrate: high-fat diet. But it can be arrested immediately by giving the patient a high-carbohydrate: low-fat diet. I have under my care at present three cases in which by this means the progress of early diabetic cataracts has been completely arrested for four and a half, three, and one and a half years respectively. Such cataracts develop only in untreated or badly treated diabetics; pulmonary tuberculosis develops frequently in similar cases. It appeared to me that the metabolic disturbance which was responsible for the production of the cataract might be the same or related to the disturbance which produced susceptibility to tuberculosis, and that, therefore, the measures which produced such a dramatic arrest of cataract development might also benefit the patient's resistance to tuberculosis. The results have justified this expectation.

Two cases whose radiograms are reproduced at the end of this paper may be cited as examples in support of this claim. The first case (No. 10, Table II) (Plate 26, Figs. 4 a, 4 b, and 4 c) on admission showed infiltration in the right lung and perihilar consolidation with a cavity in the left lung. After three months in bed, receiving this type of diet and sufficient insulin, but no

TABLE III

*Example of 2,500 Calorie Diet for Diabetics with Pulmonary Tuberculosis*

		Carb.	Prot.	Fat.
<i>Breakfast</i>	Grape fruit or orange 3 oz. and sugar 1 level teaspoonful	6	—	—
	Milk 5 oz., coffee	5	—	—
	Bacon 1 oz.	7½	5	5
	1 egg	—	5	15
	Bread 2 oz.	—	6	5
	Marmalade 1 oz., butter ¼ oz.	30	2	—
		25	—	6½
		73½	18	31½
<i>Lunch</i>	Meat 2½ oz.	—	22½	7
	Carrots 2 oz.	3	—	—
	Potato 4½ oz.	27	2	—
	Butter ½ oz.	—	—	6½
	Custard (1 egg, milk 5 oz.)	7½	11	10
	Banana 3 oz.	18	—	—
	Lemon juice + 4 level teaspoonssugar	20	—	—
		75½	35½	23½
<i>Tea</i>	Tea, milk 2 oz.	3	2	2
	Bread 2 oz.	30	2	—
	Butter ½ oz.	—	—	12½
		33	4	14½
<i>Supper</i>	Meat 2 oz.	—	20	6
	Greens 3 oz.	1	½	—
	Potato 4 oz.	24	2	—
	Butter ½ oz.	—	—	6½
	Milk pudding (cereal ½ oz., milk 7 oz.)	23	7	7
	Coffee + milk 2 oz.	3	2	2
	2 cream crackers	10	—	—
		61	31½	21½
<i>9 p.m.</i>	Milk 7 oz. + 2 cream crackers	20	7	7
During 24 hours 1 pint of fruit drink containing 60 gm. carbohydrate (lemon and sugar 2 oz.)		60	—	—
Total		323	96	98
Calories		2,558		

treatment at all of any other kind, no signs of tuberculosis could be detected in either lung. The second case (No. 5, Table II) (Plate 25, Figs. 3 a, 3 b) received this diet and insulin, ceased work, and remained at home, but did not rest in bed. The subclavicular infiltration disappeared completely in eight months.

The diet used was of relatively high caloric value. The smallest diet in the series was of 2,000 calories, and the highest diet was about 2,600 calories. The three main component foodstuffs were roughly in the proportion of carbohydrate 3, protein 1, fat 1. In such a diet the fat content does not exceed 100 gm. and I have thought it an advantage to secure an

adequate supply of vitamins A and D by giving in addition half a drachm of 'Haliverol' or of 'Radiostoleum' daily. An example of such a diet is given in Table III.

The belief that a high-calorie : high-carbohydrate diet is the best for diabetics with pulmonary tuberculosis is supported by a survey of the literature. It can there be seen that those clinics and sanatoria from which high mortality rates have been reported were on the whole institutions in which diets restricted in carbohydrate and usually low in calories were used (Rosenberg and Wolf, 1927; Fitz, 1930; Wiener and Kavee, 1936). On the other hand, the clinics reporting more favourable results have been those using higher carbohydrate and usually high calorie diets (Kutschera-Aichbergen, 1931; Vrhovac, 1937). A strong indictment of the application to diabetics with associated pulmonary tuberculosis of the old orthodox principle of diabetic therapeutics—under-nutrition—has been made by Fishberg (1932). He states that patients submitted to this régime, in which low-calorie : low-carbohydrate diets are used, certainly often lose their glycosuria, but that at the same time a rapid progress of the pulmonary tuberculosis occurs; and he even states that such starvation may provoke the appearance of exudative lesions.

The results of giving the new diet to our diabetics with pulmonary tuberculosis was so unexpectedly good that I decided to try the effect of similar diets and insulin on non-diabetic cases of early pulmonary tuberculosis. A régime comprising a 4,000 calorie diet with about 600 gm. of carbohydrate and insulin in six 10 unit doses daily was devised. The progress on the few cases tested was satisfactory, and Day and Pearson (1937), who have used this régime at Mundesley Sanatorium, report good results. It is possible that high-carbohydrate diets influence the metabolism of the body in a way unfavourable to the invasion of the tubercle bacillus and that low-carbohydrate diets and under-nutrition, which influence the metabolism of the body in a manner similar to diabetes mellitus, have the reverse effect.

*Insulin.* The early days of the use of insulin in diabetic cases with associated pulmonary tuberculosis were marked by a peculiar controversy. One school of thought maintained that insulin should be used in amounts adequate to control the diabetes, the other that insulin was dangerous as it tended to cause tuberculous lesions to flare up. As late as 1932 Fishberg made the remarkable statement that insulin fails in diabetics with tuberculous complications and should be given only to such cases as an emergency life-saving remedy. The eminence of the author requires that such a statement be considered carefully. An explanation suggested is that the earlier preparations of insulin contained impurities which were capable of provoking allergic reactions in tuberculous lesions. When one considers, however, Fishberg's recorded experience that under-nutrition provokes activity in quiescent tuberculous lesions, the explanation arises that the flaring up of lesions, which Fishberg attributed to insulin, might actually have been due to the concomitant use of low-calorie : low-carbohydrate diets. There may, however, be an element

of truth in the objection. In two cases I have suspected that a severe hypoglycaemic attack had an unfavourable effect upon the pulmonary lesions. Be that as it may, the controversy seems to be dying, for all the recent reports deny any untoward effect of insulin.

Insulin should be given to all diabetics with pulmonary tuberculosis. Usually there is no choice in the matter because tuberculosis appears chiefly in the severe diabetics. All the cases that I have seen have required moderate or even large doses of insulin, but in practically every case, when improvement commenced in the pulmonary lesion and the clinical signs of toxæmia lessened, it has been possible to decrease the dose, although in no case has the patient been able to dispense with insulin entirely. The amount of insulin required is determined by the requirements of each individual case. There is no limit to the dose that can be given other than the satisfaction of the patient's needs. Recently several cases have been given Zinc Protamine Insulin after control had first been established with ordinary insulin. The results were as satisfactory as in cases of diabetes uncomplicated by pulmonary tuberculosis, and no modification in the technique of administration of the new type of insulin was required (Himsworth, 1937).

*Balancing.* In the balancing of the tuberculous diabetic, modifications are necessary in the orthodox scheme of treatment owing to the necessity of bringing the diabetes quickly under complete control, so as to retard the spread of the tuberculous lesion at the earliest possible moment. To this end no attempt should be made to build up the patient's diet from one of low to one of high caloric value, nor should any attempt be made to spare the patient insulin injections. The full diet should be given from the beginning of treatment and ordinary insulin should be given first in three doses daily and later, if necessary, increased to six doses or even more. The introduction of insulin into therapeutics removed the justification for constructing diabetic diets on the basis of a certain number of calories and a certain number of grammes of carbohydrate or of fat for each kilogramme of body weight. The proportions of the three main foodstuffs in the diet of diabetics with pulmonary tuberculosis have already been discussed; the caloric value of the diet can be decided by a glance at the patient. A small individual should be given a 2,000 calorie diet, a large individual a 2,600 calorie diet. More than this amount is seldom required to make the patient gain weight. If there is much toxæmia, the patients may be unable to ingest this amount of food in a solid form. In that case a fluid or semi-solid diet should be devised containing the full amount of carbohydrate, but reduced amounts of protein and fat. Later, as appetite improves, this diet can be slowly changed to contain the more solid foods.

When the patient first comes under treatment the urine usually contains much sugar and ketone bodies. The first object is to eliminate the ketones. If the ketone bodies are so abundant as to give a positive reaction with the ferric chloride reagent, the patient should be treated as a case of incipient coma (Himsworth, 1932). If, however, ketones are not present in such large amounts, the diet should be commenced at once. Insulin should then be

given immediately; if the nitroprusside reaction in the urine is positive, in doses of 20 units three times a day; if this reaction is negative, in doses of 10 units three times a day. If at the end of twenty-four hours on the diet and insulin, the ketonuria has not disappeared, then 30 gm. of sugar in the form of a lemonade and 10 units of insulin should be given at mid-morning, mid-afternoon, and midnight. In the presence of much toxaemia further increase in insulin dosage may be necessary. As soon as the urine shows signs of becoming free from sugar, the doses must naturally be decreased, and if insulin and sugar are being given between meals these should first be removed. By these means a diabetic can rapidly be brought under control and, by close attention to the results of urine testing and to the patient's symptoms, hypoglycaemia can be avoided. The chemical criteria of satisfactory control should be a urine consistently free from ketone bodies and either free of sugar or containing the smallest amount of sugar that the patient can tolerate without experiencing hypoglycaemic symptoms. Some diabetics with pulmonary tuberculosis are difficult to stabilize. Fluctuations of toxaemia produce corresponding fluctuations in glycosuria. In such cases it is useful to give half the dose of insulin required in the form of Zinc Protamine Insulin before breakfast, and the other half in three doses of ordinary insulin, one before each of the three main meals. In this way the inrush of sugar after meals is controlled by ordinary insulin whilst the Zinc Protamine Insulin maintains a steady 'basal' control of the patient during the whole day.

#### *Treatment of the Pulmonary Tuberculosis*

*General.* Measures to promote the general health of the tuberculous patient are as important in the diabetic as in the non-diabetic patient, and in an early case these, in conjunction with control of the diabetes, will often suffice to effect an apparent cure. The value of fresh air is difficult to assess, although there is no doubt that it increases the patient's subjective sense of health, and, in so far as it promotes a regular appetite, is of help in the treatment of the diabetes. But whether it is of great importance or not, doubt may be felt. One of the patients of our series apparently recovered completely from a tuberculous hilar pneumonia after three months spent in a general ward of a London hospital, and four other patients who showed satisfactory progress continued to live in the centre of London. Fresh air would, therefore, seem to be advisable, but not essential, to successful treatment.

Rest is undoubtedly of great value, and the following case (No. 2, Table II) illustrates this point. The patient, a boy, aged 15, was found to have a small lesion at the left base. With treatment of the diabetes this apparently regressed and the patient was allowed to return to his home in a London suburb. Whilst there he faithfully observed his instructions regarding hours of sleep and rest, and three months after the diagnosis was made the lesion was fast disappearing. Six weeks later he felt so well that he was allowed to start work in a shop. Within a fortnight he began to pass sugar in his

urine, and an X-ray taken seven weeks after starting work showed a pneumonic type of consolidation and a cavity in the lower lobe of the left lung. Diet and insulin had remained the same throughout until the insulin was increased by 10 units a fortnight before the last X-ray. Less clear-cut, but similar, cases have stressed this lesion, and now a point is made in early cases of offering the patient a choice between some months in hospital or rest at home with cessation of work. The majority to whom the choice is permitted choose the latter alternative, and so far there is no reason to regard the method as ineffective.

Considerations of fresh air and rest naturally raise the question of sanatorium treatment. Theoretically this should be ideal, but in practice it is not usually so. Its failure can largely be attributed to the fact that the majority of sanatoria do not make special arrangements for dealing with cases of diabetes mellitus. This is mainly attributable to the authorities not having realised that when pulmonary tuberculosis and diabetes mellitus are associated the treatment of the diabetes mellitus is of primary importance. Many of these institutions are not equipped to dispense diabetic diets, and unless the patient himself is competent to check the diet, and has the hardihood to do so, it is probable that he will not regularly receive the diet prescribed nor have his insulin properly adjusted to his changing needs. The result is that patients may return from sanatoria no better than when they went, on inadequate doses of insulin and taking diets which have long ceased to be used in modern diabetic clinics. At present it is no exaggeration to say that it is far better for a diabetic with tuberculosis to be treated in a general ward of a London hospital than to go to a sanatorium, unless his physician has personal knowledge that he can there receive efficient treatment.

*Special treatment. Artificial pneumothorax.* Good results from the use of artificial pneumothorax have been reported by Dorendorf (1928), Root (1934), Myers and McKean (1936), Vrhovac (1937), and Wiener and Kavee (1936). It has been used in eight of the present cases. One of the patients is dead, but from her wanton disregard of treatment little else could be expected. Of the other cases, in one, whose lung was permitted to re-expand three years ago, the disease is apparently cured, one has fibrosis of the lung, two are rapidly improving, two are stationary, and one, who refused further refills two years ago, is slowly deteriorating. From this small number of cases little knowledge can be gained, but a tentative opinion may be expressed with regard to the use of this treatment in cases with the hilar pneumonic spread. The case whose X-rays are shown in Plate 26, Figs. 4a, 4b and 4c, recovered without such special treatment, and emboldened by this result it was decided to try the effect of diet and insulin alone upon another case of this type. In this case the pneumonic spread had reached the pleura posteriorly. After six weeks' rest in bed and treatment of the diabetes, the X-ray showed no change in the condition, so an artificial pneumothorax was induced. It was then found that an adhesion had formed at the site where the pneumonic process had reached the pleura, and also at the base. The upper adhesion eventually

broke, an effusion resulted and was reabsorbed, but the basal adhesion held and prevented the collapse of a cavity. Phrenic avulsion was then performed and the cavity collapsed. From this time the diabetes proved less difficult to control and the patient's condition improved. I am therefore of the opinion that in cases of the hilar-pneumonic type artificial pneumothorax should be induced as soon as possible.

*Phrenic avulsion.* Phrenic avulsion has been performed on only two patients. In one it had no effect; the favourable result in the other has been recorded above.

The treatment of diabetics with pulmonary tuberculosis can now conveniently be reviewed. It is of primary importance to control the diabetes, and to this end a high-carbohydrate : high-calorie diet and insulin in doses adequate to keep the urine always free from ketone bodies, and if possible usually free from sugar, should be given. Cessation of work and long hours of rest are essential in all cases, and it is probably of advantage for the patient to live as much as possible in the open air.

Early cases, who whilst ambulant have a normal temperature, pulse-rate, and sedimentation-rate, and in whom the X-ray reveals small lesions not at the surface of the lung, may be treated at home. It must be insisted, however, that such cases attend at frequent intervals for regulation of their diabetic treatment and for further X-ray examinations of the chest. Should the X-rays reveal that the pulmonary lesion is progressing, they must be treated like the more serious cases. The more serious cases who show signs of tuberculous toxæmia or in whom the X-rays reveal more extensive involvement of the lung tissue should be admitted to hospital and confined to bed. Special measures directed against the pulmonary tuberculosis may then be undertaken if necessary.

In conclusion, I would state that if the diabetes of tuberculous diabetics is efficiently controlled there are grounds for endorsing Root's (1934) suggestion that 'the prognosis in pulmonary tuberculosis in diabetics may be better than in non-diabetics, if they are discovered at relatively the same stage of tuberculosis'. Such a statement, although conflicting with previous clinical experience, is no more than could be expected from theoretical considerations. Diabetes predisposes to the development of tuberculosis, and when this predisposition is removed by treatment the diabetic is in a relatively stronger position than the non-diabetic whose general resistance was so poor that he developed a similar lesion although not under the handicap of diabetes.

#### *Summary*

1. Pulmonary tuberculosis was found in 15 (6.5 per cent.) of 230 consecutive cases of diabetes mellitus on their first attendance at hospital. Two of these cases had tuberculous broncho-pneumonia and were readily diagnosed by clinical methods. In the remaining 13 cases the diagnosis was made only

by radiological examination. The conclusion is drawn that early pulmonary tuberculosis in the diabetic is impossible to diagnose by clinical methods and that a routine radiogram of the chest is essential in every diabetic when he is first seen. The X-ray examination should ideally be repeated every year, or more often if the control of the diabetes is unsatisfactory.

2. The radiological appearances of early pulmonary tuberculosis in diabetics are discussed.

3. The association of diabetes mellitus and pulmonary tuberculosis is reviewed. Evidence is brought forward that uncontrolled diabetes predisposes to the development of the pulmonary lesion, and conversely that treated diabetics are no more liable to develop pulmonary tuberculosis than non-diabetic subjects.

4. The favourable results of treatment in 29 cases (including the 15 above) of pulmonary tuberculosis complicating diabetes mellitus, and the methods of treatment used are recorded. Evidence is presented that when these two diseases are associated the treatment of the diabetes is of primary importance.

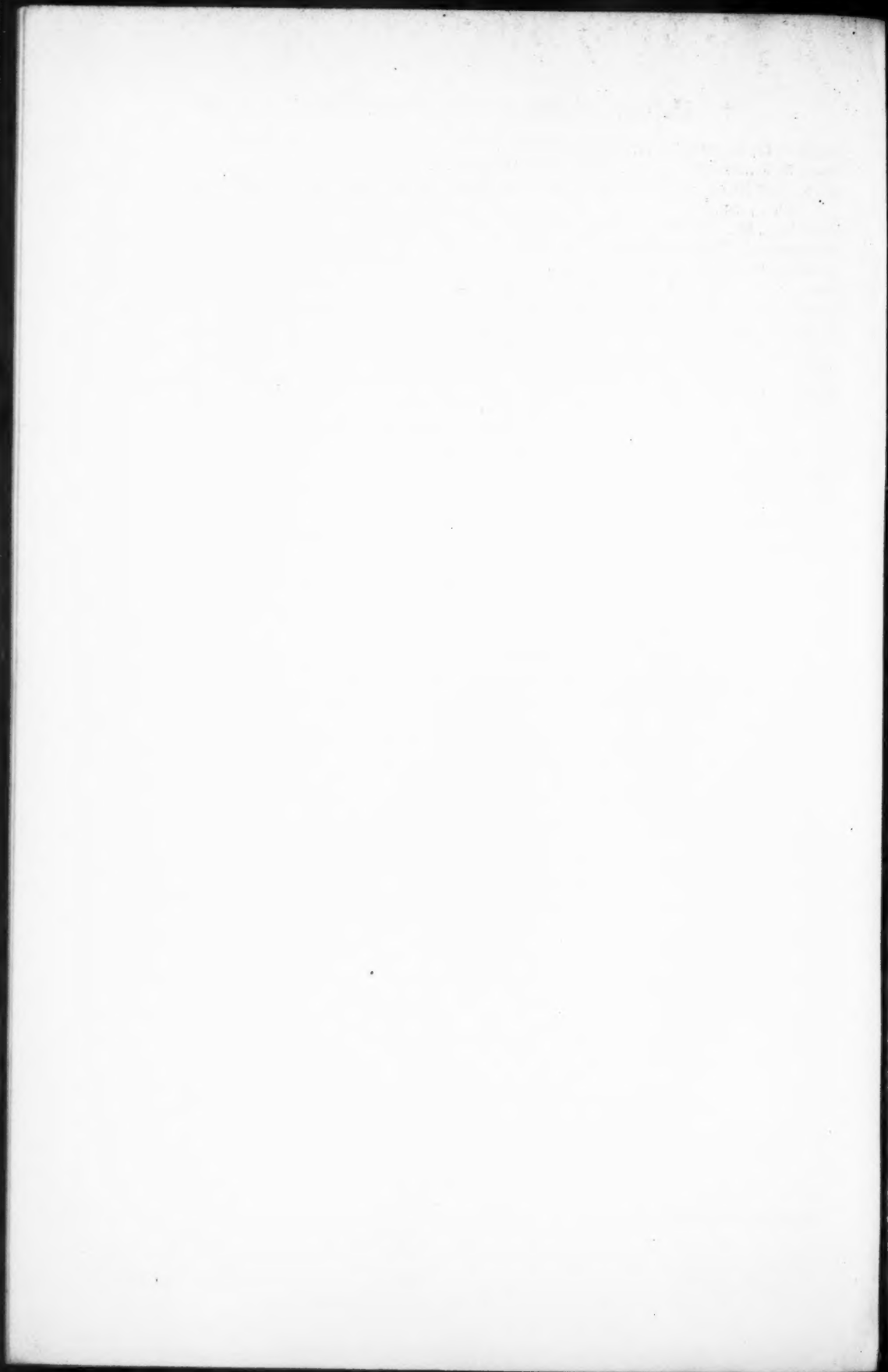
5. It is concluded that the prognosis in diabetics with pulmonary tuberculosis is excellent if the pulmonary lesion is discovered at an early stage.

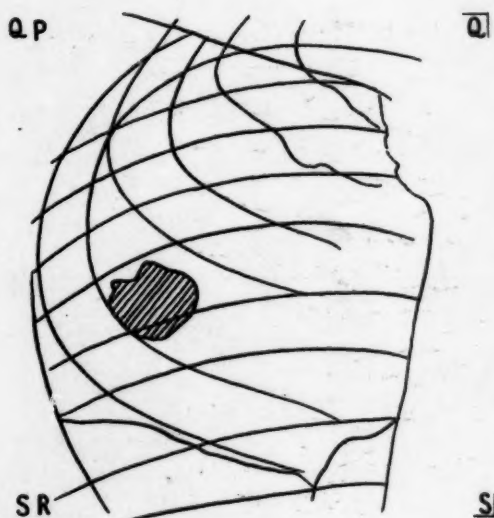
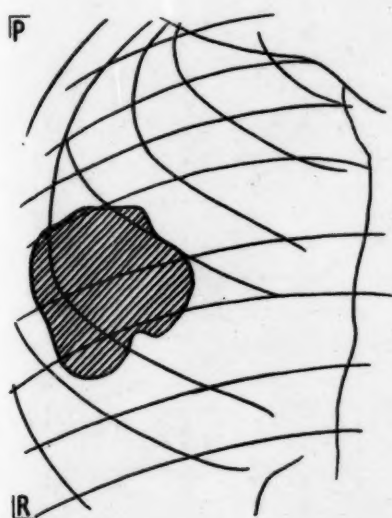
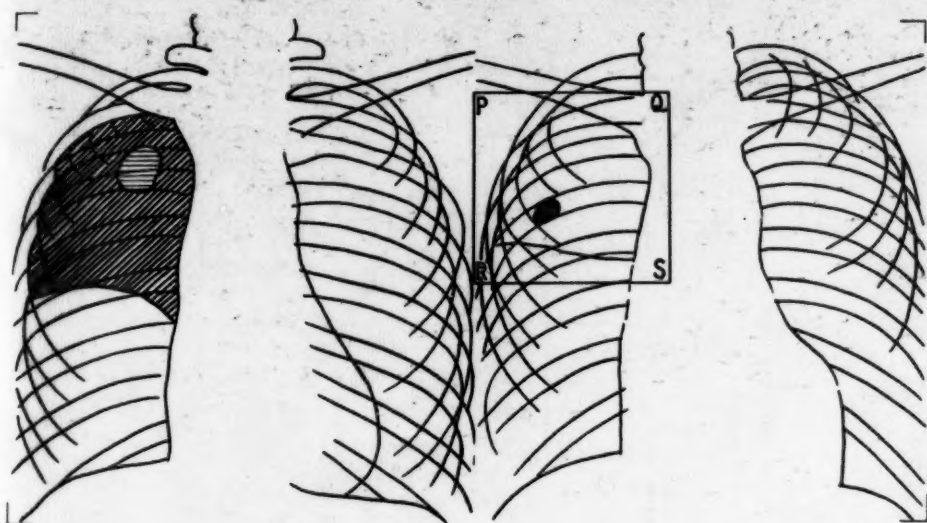
I should like to thank Dr. Gwen Hilton of the Radiological Department, University College Hospital, for her help in interpreting the radiograms.

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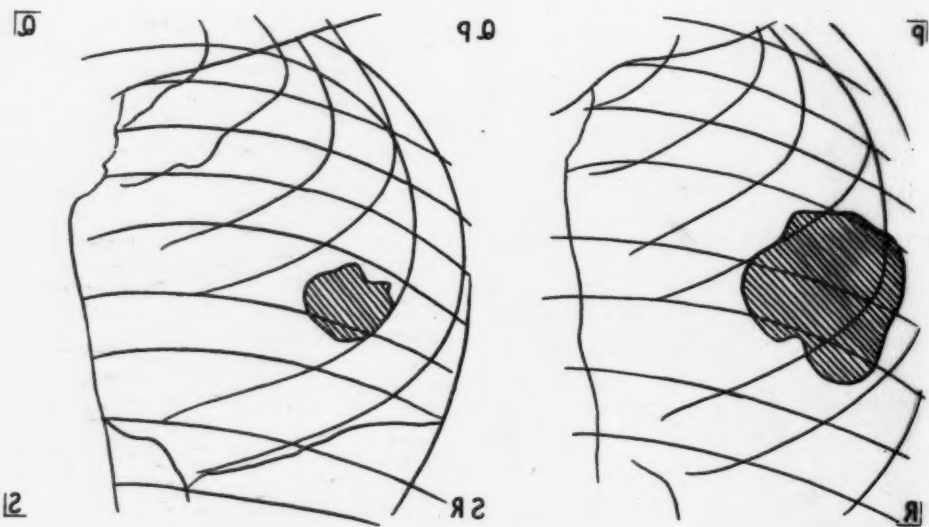
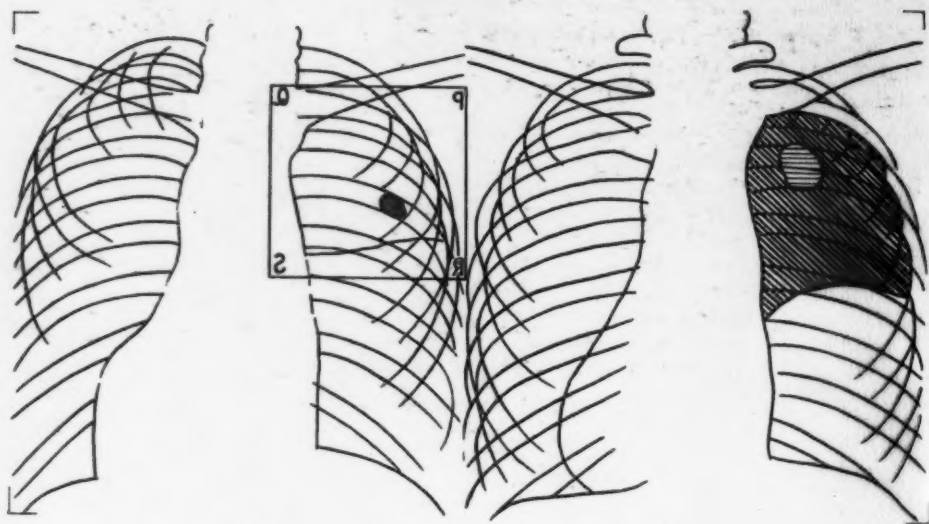
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Oblique shading = infiltration.

Horizontal shading = cavitation.



Horizontal shading = cavitation.

Oblique shading = infiltration.

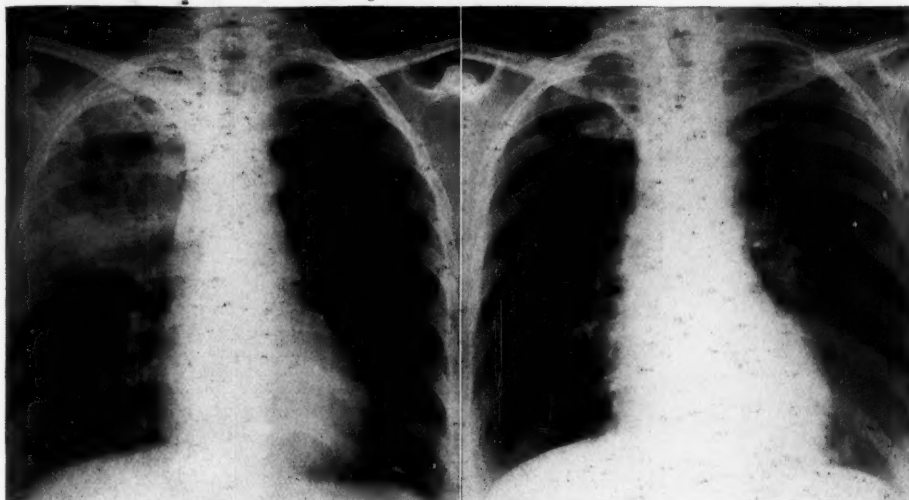


FIG. 1a on 10. 2. 33, showing cavity and surrounding infiltration in the upper half of the right lung

FIG. 1b on 31. 10. 33. Disappearance of infiltration, cavity not visible. A faint patch of mottling in the second interspace nearer the periphery than the mediastinum can be seen

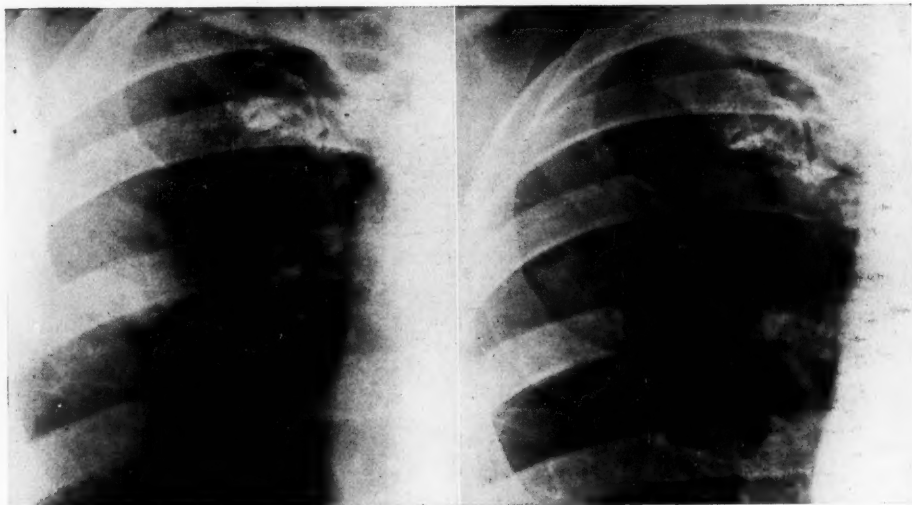
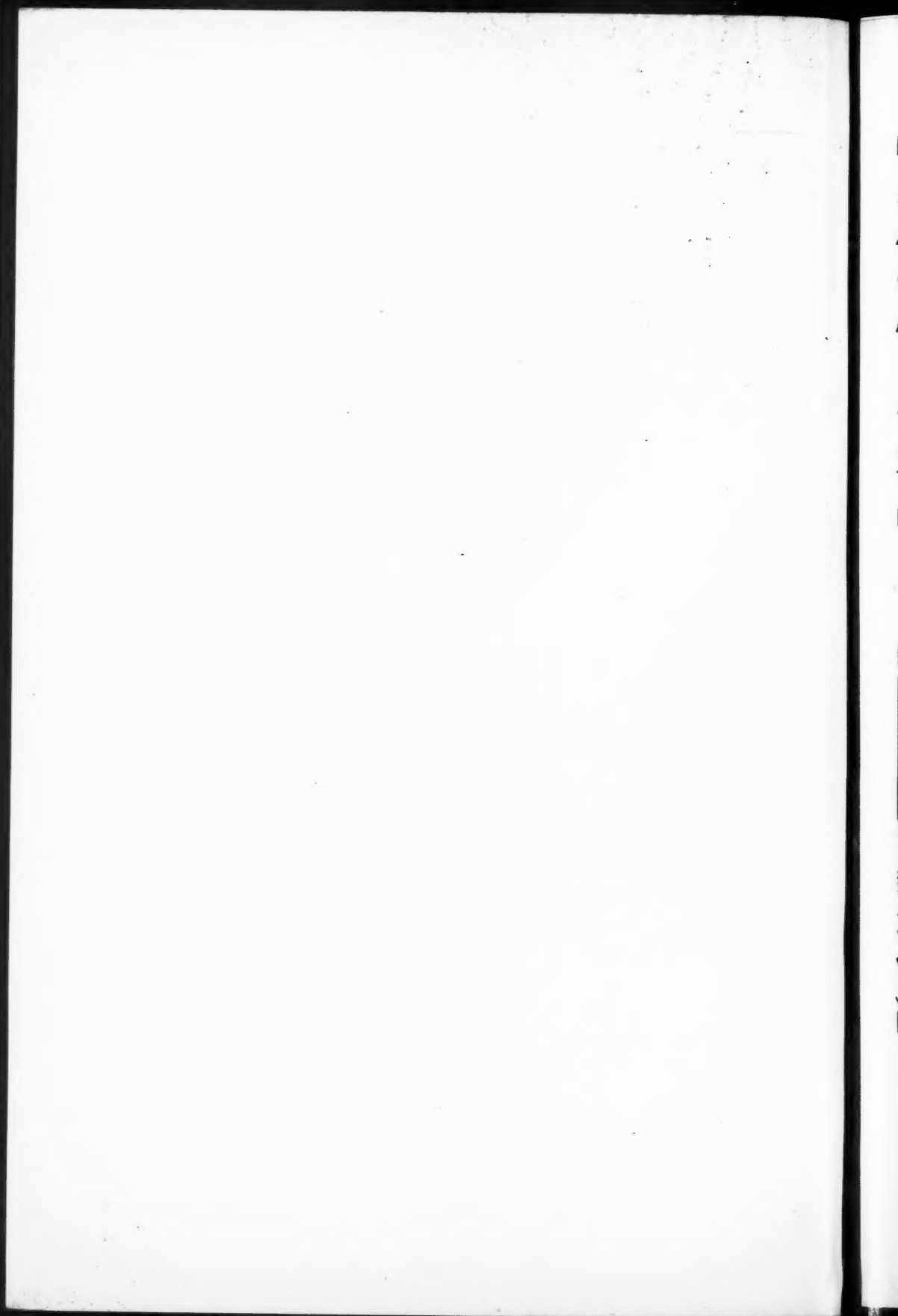
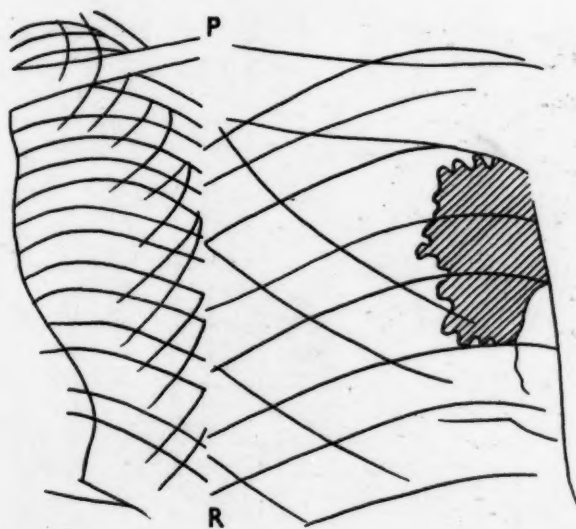
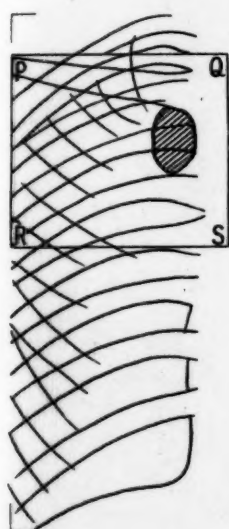
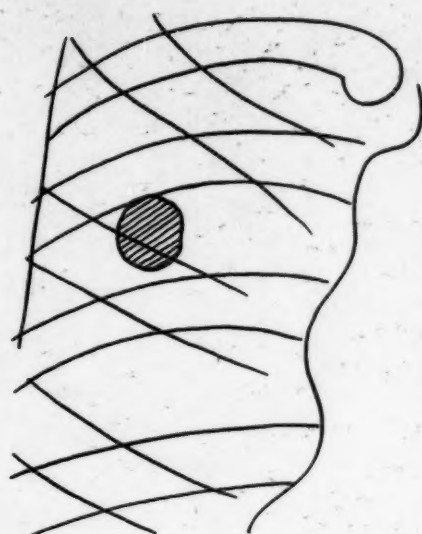
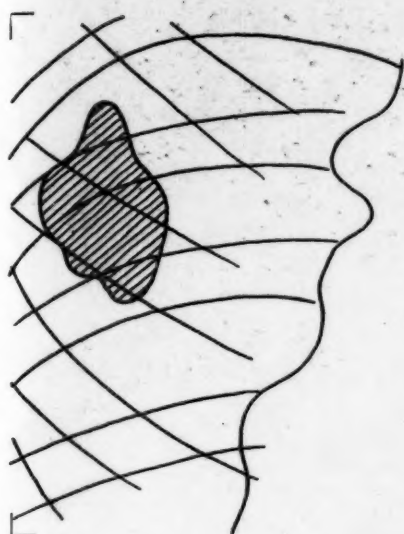


FIG. 1c on 30. 4. 34. Direct contact print of upper half of right lung from the same case (area included in the square on the tracing of Fig. 1b). Recrudescence with area of smooth infiltration involving the lateral part of the lung in the first and second interspaces

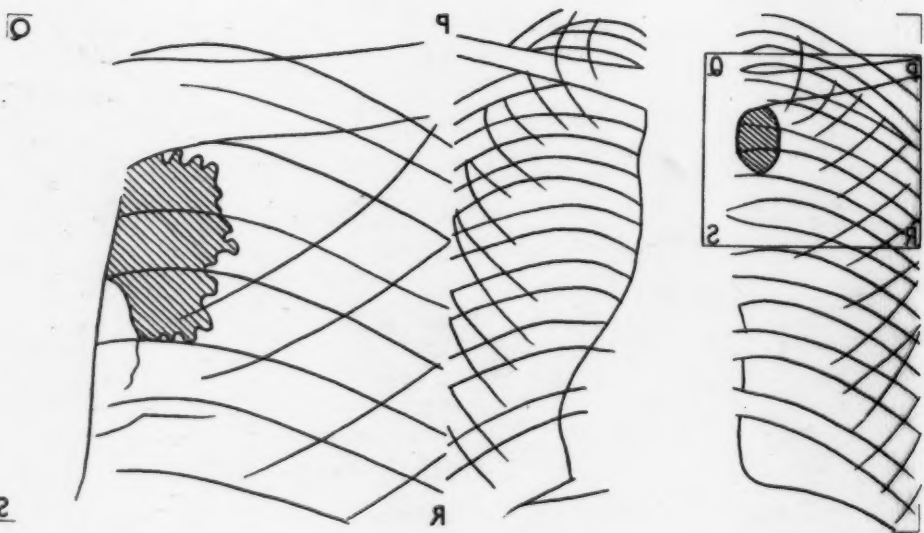
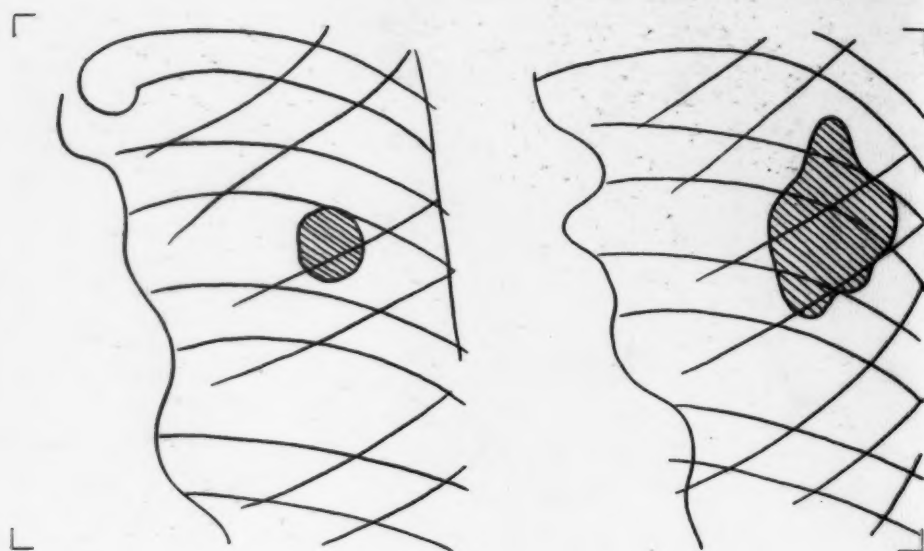
FIG. 1d on 15. 8. 35. Direct contact print of same area as Fig. 1c, showing condensation of the diffuse infiltration to a homogeneous circular shadow

All from the same case, A.V. (page 378), an established case of pulmonary tuberculosis





Oblique shading - infiltration.



Opilone shading - infiltration.

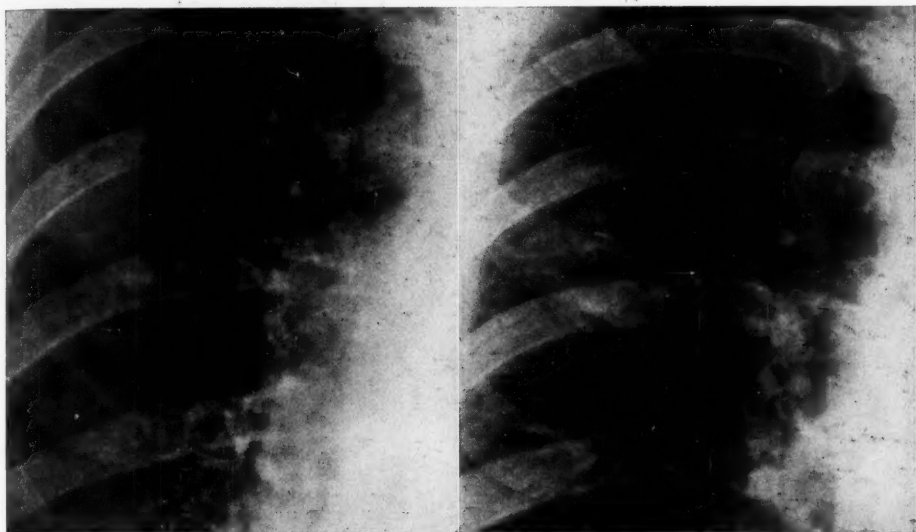


FIG. 2a on 15. 6. 36. Upper half of right lung. Ill-defined patch of confluent mottling centred on the upper edge of the third rib peripherally

FIG. 2b on 30. 3. 37. Showing condensation of the diffuse mottling into a circular and more uniform patch

Figs. 2a and 2b from Case 8, Table II (page 379). Direct contact prints to show the consistency of the lesion

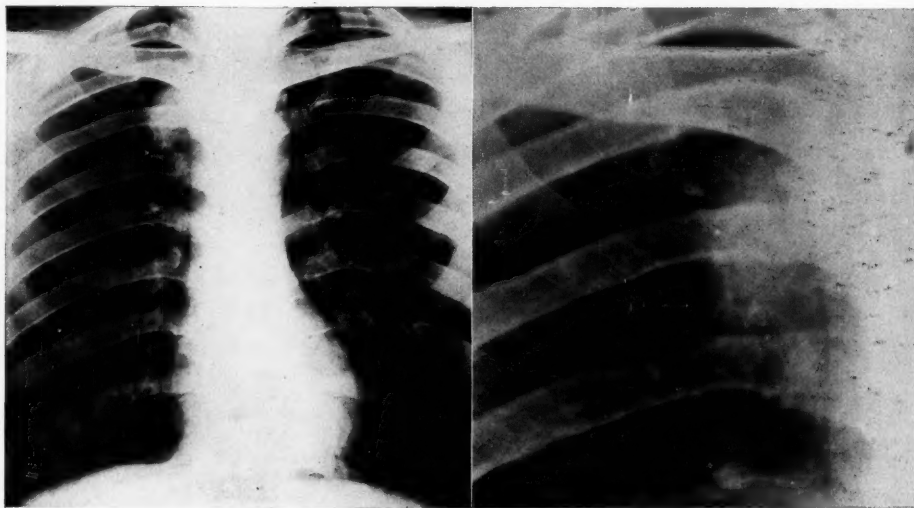
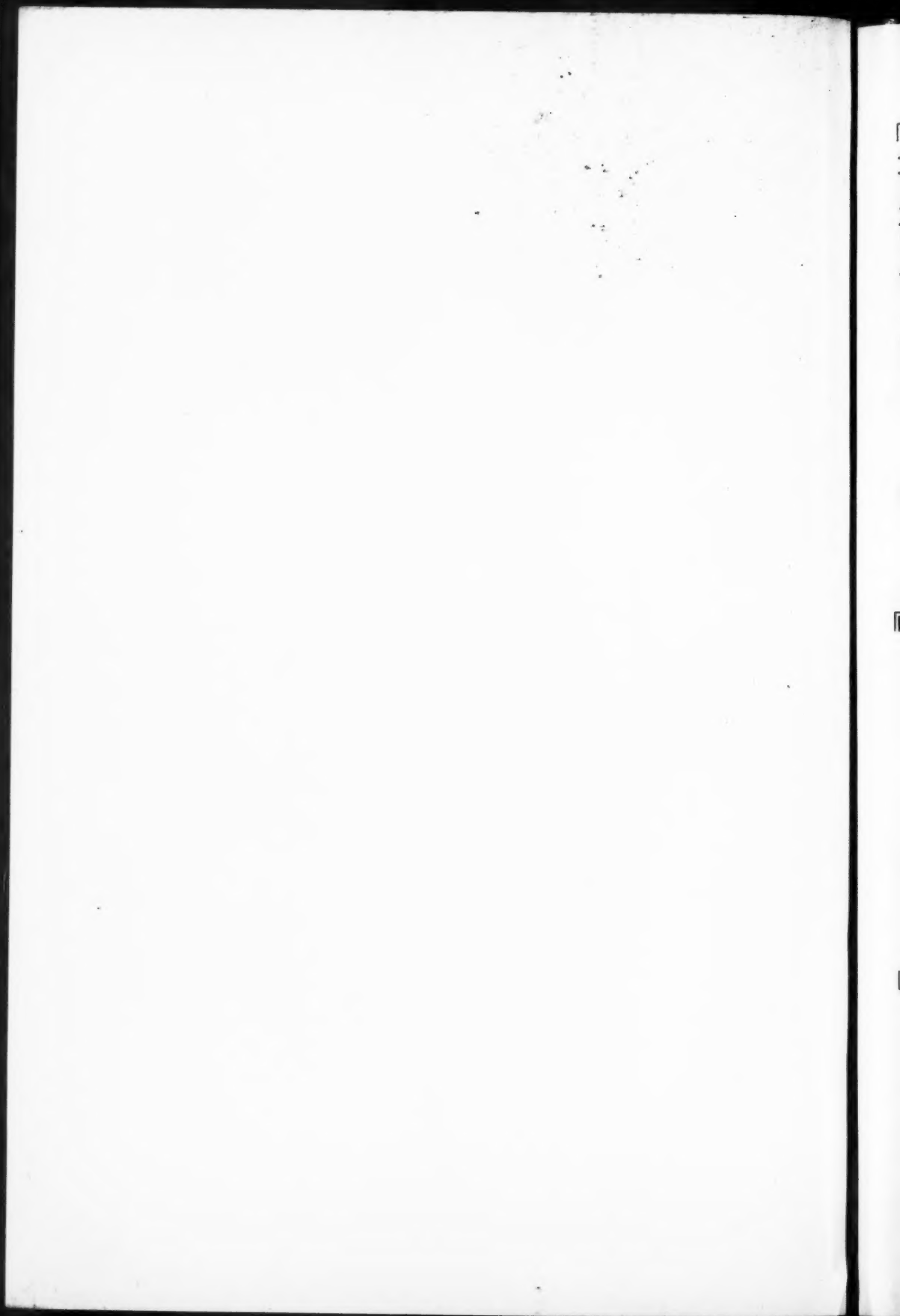
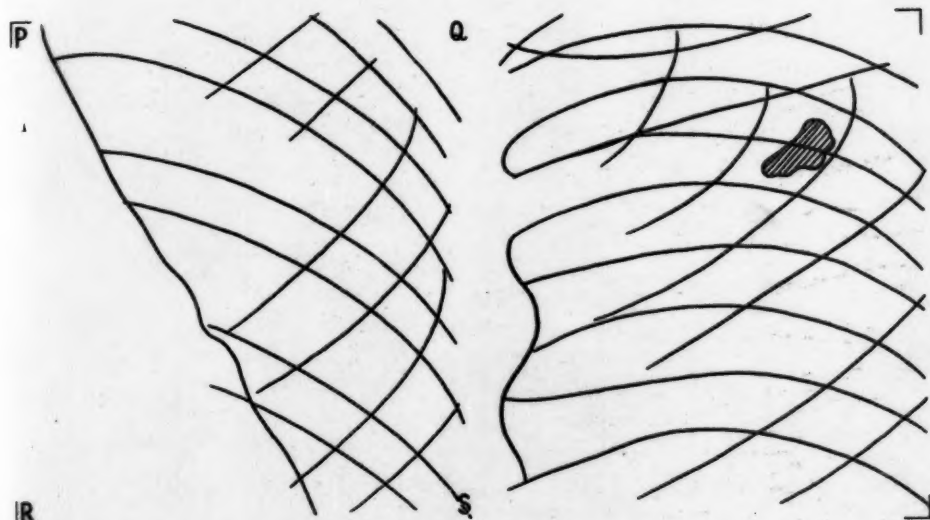
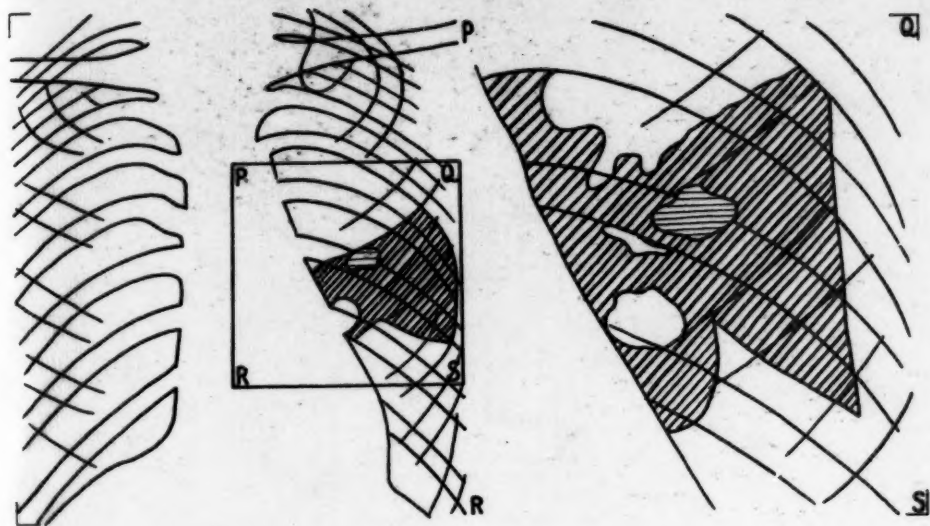


FIG. 3a on 12. 8. 36. Ovoid area of infiltration below inner end of right clavicle

FIG. 3b on 12. 8. 36. Direct contact print of the area included in the square on the tracing of Fig. 3a to show the consistency of the lesion

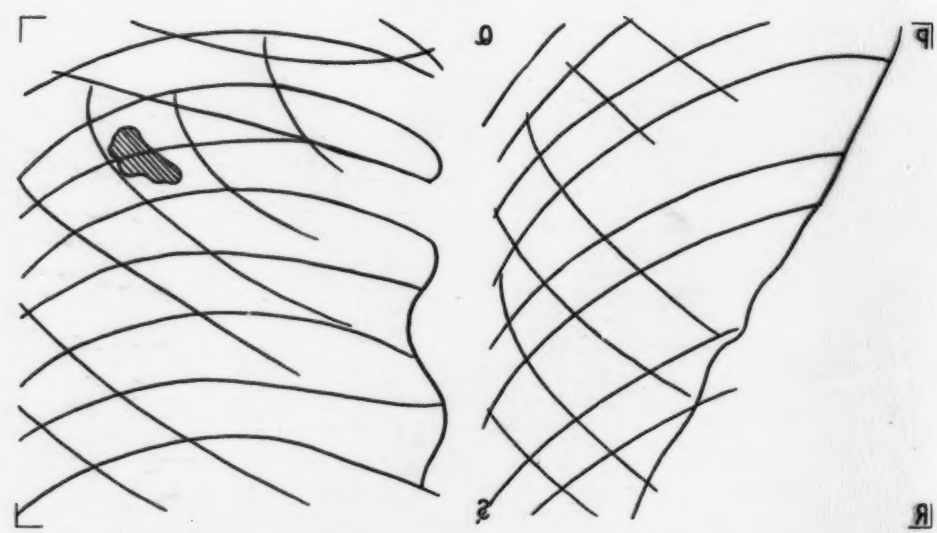
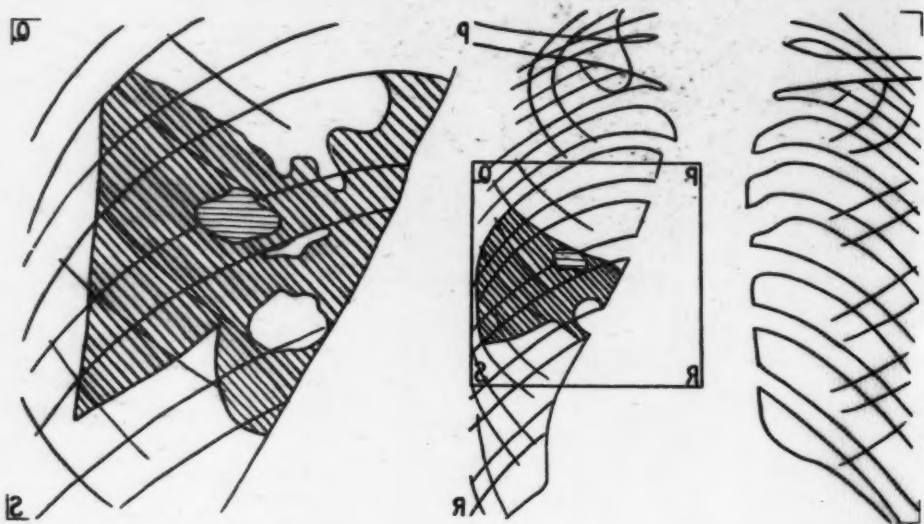
Figs. 3a and 3b from Case 5, Table II (p. 379)





Oblique shading - infiltration.

Horizontal shading - cavitation.



Horizontal shading - cavitation.

Oblique shading - infiltration.

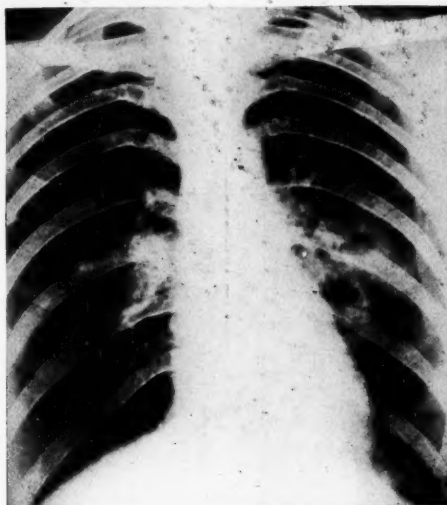


FIG. 4a on 25.5.37. Smooth infiltration spreading from the left hilum in the centre of which is a cavity. In the actual X-ray a faint mottling can also be seen on the right side round the calcified patch in the third interspace

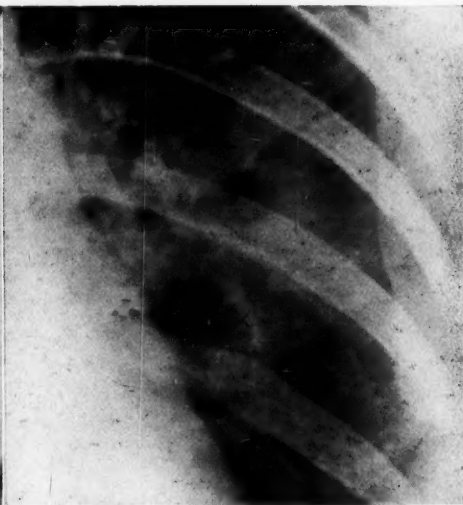


FIG. 4b on 25.5.37. Direct contact print of the left hilar area, demarcated by the square on the tracing of Fig. 4a, to show the details of the hilar lesion



FIG. 4c on 9.9.37. Direct contact print showing disappearance of the lesion shown in Fig. 4b



FIG. 5. X-ray of upper half of left chest to show early lesion in the lateral portion of the first interspace

Figs. 4a, 4b, and 4c from Case 10, Table II (page 379).

FIG. 5 from Case 4, Table II (p. 379)



## THE ROLE OF COPPER IN IRON-DEFICIENCY ANAEMIA IN INFANCY<sup>1</sup>

By JAMES H. HUTCHISON.

(From the Department of Medical Paediatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

### *Introduction*

RECENT investigations have yielded conflicting results as regards the efficacy and mode of action of copper in the treatment of the hypochromic group of the anaemias. Research in this subject has been along two lines, comprising on the one hand animal experiment, and on the other the trial use of copper in the treatment of anaemia occurring in the human subject. In 1925 Hart, Steenbock, Elvehjem, and Waddell showed that iron alone was inadequate to bring about regeneration of haemoglobin in rabbits, previously rendered anaemic by milk feeding. On the other hand, fresh cabbage or iron-free chlorophyll in the presence of inorganic iron ( $\text{Fe}_2\text{O}_3$ ) rapidly cured the anaemia. In 1927 Hart, Elvehjem, Waddell, and Herrin demonstrated that vitamin E was not the factor supplied by the cabbage, etc., and that while pure ferrous sulphate was ineffective, impure ferrous sulphate was quite efficient, a fact which may explain a large number of the discrepancies in the results of other workers. Having demonstrated (Waddell, Steenbock, Elvehjem, and Hart, 1928) the suitability of the rat for studies in anaemia, they further showed that the other factors necessary in addition to iron were of an inorganic nature, because the *ashed* residues from dried beef liver, dried lettuce, and yellow corn were effective in curing anaemia (Waddell, Elvehjem, Steenbock, and Hart, 1928*b*). Their subsequent work on the rat, scrupulously controlled at every step, has shown that for the cure of 'milk anaemia' both iron and traces of copper are essential (Hart, Steenbock, and Elvehjem, 1928; Waddell, Steenbock, and Hart, 1929*a*, 1929*b*; Waddell, Steenbock, Elvehjem, and Hart, 1929). The same holds good for an analogous anaemia in chicks given milk and a cereal low in iron and copper (Elvehjem and Hart, 1929). That copper occurs in vegetable materials used as foodstuffs had, of course, been known for some time (Meissner, 1816; Maquenne, and Demoussy, 1920; Guérithault, 1920), but until 1928 no physiological function had been assigned to it.

McHargue, Healy, and Hill (1928), Becker and McCollum (1930), Keil and Nelson (1931), Wickwire, Burge, and Krouse (1936), Stein, Radetsky,

<sup>1</sup> Received March 12, 1938.

and Lewis (1936), and Lewis, Weichselbaum, and McGhee (1930) have all confirmed this effect of copper. Beard, Myers, and Shipley (1929) and Mitchell and Miller (1931) have claimed, however, that purified inorganic iron alone would slowly cure the anaemia of the rat, and Hart, Elvehjem, Steenbock, Kemmerer, Bohstedt, and Fargo (1929) have demonstrated that in the nutritional anaemia of suckling pigs, iron alone stimulates haemoglobin synthesis as well as iron supplemented with copper. They suggest that this may be due, either to the fact that their pigs had some undetected available source of copper, or that in pigs an iron deficiency occurs before there is any copper deficiency. Robscheit-Robbins and Whipple (1930) have found that the action of copper alone in curing anaemia in dogs is uncertain, and without question is far less potent than iron. Their conclusions are, however, not directly comparable with those of the Wisconsin workers, because the former produced the anaemia by repeatedly bleeding the dogs, whereas the 'milk anaemia' of the rats used by the latter workers was a true nutritional anaemia produced by a deficiency of food factors. Further support is given to those who stress the importance of copper in haemoglobin synthesis, by the finding that the anaemia which is common among yearlings and heifers' suckling calves in Florida responds rapidly to ferrous ammonium citrate fortified with copper sulphate, but that iron supplements alone have proved inadequate (Neal, Becker, and Shealy, 1931).

In 1928, Titus, Cave, and Hughes produced evidence which seemed to indicate that, in the rat, manganese added to a milk-iron diet gave almost as good results as did copper given in the same way, and they suggested that there was a group of substances, rather than a single substance, which is active in haemoglobin building. These workers later confirmed their original contention (Titus and Hughes, 1929), and showed that the same applied to the rabbit (Titus and Cave, 1928). Beard, Myers, and Shipley (1929) also found that cobalt, nickel, and germanium were as good supplements as copper, and later added to these several other elements possessing similar properties, e.g. arsenic, manganese, titanium, zinc, selenium, etc. (Beard and Myers, 1930). Nevertheless, Lewis, Weichselbaum, and McGhee (1930) obtained no haemoglobin regeneration when iron plus manganese or iron plus cobalt were fed to rats, although they confirmed the potency of copper in this respect, and Krauss (1931) obtained no better results with iron plus copper plus manganese than with iron plus copper. Keil and Nelson (1931) found the following elements to be inactive as supplements to iron in the treatment of 'milk anaemia' in the rat; vanadium, titanium, manganese, nickel, arsenic, germanium, zinc, chromium, cobalt, tin, and mercury, although they too confirmed the potency of copper in this respect. Waddell, Steenbock, and Hart (1929*b*) reported no success with twelve 'trace' elements—zinc, chromium, germanium, nickel, cobalt, mercury, lead, antimony, tin, cadmium, arsenic, and manganese—and concluded that copper is unique in this connexion, and must be considered a necessary

element in the nutrition of the animal body. Robscheit-Robbins and Whipple (1930) tested the effect on anaemic dogs of various mixtures of copper, zinc, aluminium, iodine, and phosphates, with and without iron, and rarely observed any increase of haemoglobin production above that to be expected from iron alone. It is clear that animal experiments regarding the efficacy of copper as an adjuvant to iron in the treatment of anaemia have yielded conflicting results. The weight of evidence suggests, however, that copper does play some part in haemoglobin synthesis, and justifies its trial as a therapeutic agent in the anaemias of the human subject. There would not appear to be sufficiently convincing evidence to justify the inclusion in the haematologists' pharmacopoeia of the other 'trace' elements mentioned.

There are several interesting analogies between iron and copper. McHargue (1925) demonstrated that the new-born calf has a store of copper in its dried liver at birth about eight times as large, weight for weight, as that which he found in the adult animal's liver, and also that on the same basis, the amount of copper in the body of a new-born rat is nearly double that in the adult rat. It appears that young guinea-pigs have no copper or iron stores (McHargue, 1925). That a considerable storage of copper occurs in intra-uterine life has been shown in the case of the human being as well as in lower animals (Morrison and Nash, 1930; Cunningham, 1931), and analyses of infant cadavers have revealed that smaller amounts of copper are found in the livers of anaemic infants than in those of non-anaemic infants (Chou and Adolph, 1935). Furthermore, Lindow, Elvehjem, and Petersen (1929) have shown that cow's milk is low in copper as well as in iron.

These points of resemblance in the storage of iron and copper in the human infant, suggest that nutritional anaemia may, in some cases at least, be due in part to a copper deficiency, having in mind the animal experiments quoted above. As Hawksley (1934) has pointed out, two methods have been employed to demonstrate the action of copper in nutritional anaemia. One consists in prescribing iron and copper together and comparing this with iron alone; the other consists in using iron alone, and in cases not cured then adding copper. Parsons and Hawksley (1933) in a large series of nutritional anaemias, found three cases in which there was no haemoglobin response after at least six weeks of iron therapy. In each, using copper as a supplement, cure was obtained. These facts raise the question as to whether copper, being a frequent impurity in iron salts, has not played a part in the good results previously reported from iron medication. Sheldon and Ramage (1932) have shown that the distribution of copper in preparations of iron appears to be entirely inconstant. On the other hand, Davidson (1933), although accepting the conclusions of Waddell, Elvehjem, Steenbock, and Hart (1928) as to the necessity of copper as a supplement to iron in the rat, does not regard copper as of value in the human subject. In 100 Aberdeen families of the poorest classes he found that the diet contained at least 4.6 mg. of copper per diem, and in these

circumstances it was difficult to believe that small amounts of copper added to iron could be of much value. To infants, however, fed on a diet of cow's milk, which contains only very small amounts of copper, Davidson's results are not necessarily applicable.

Josephs (1931) gave iron and copper in one series of anaemic infants (aged 3 months to 2 years), and iron only in another, and found a more rapid recovery in the former group. He concluded, that for a maximum rise in haemoglobin, some factor is needed in addition to iron, and that in most cases this factor is not sufficiently supplied by the food, but is supplied by copper. A complicating factor in Joseph's series was the large number of anaemic infants with infections such as pneumonia, empyema, tuberculosis, syphilis, etc. Lewis (1931) found that iron and copper given in combination to children with nutritional anaemia were more effective than iron alone. Similar results have more recently been reported by other workers (Goldstein, 1935; Elvehjem, Duckles, and Mendenhall, 1937). Mills (1930) obtained similar results in adults, which are difficult to reconcile with Davidson's (1933) estimation of the copper content of the adult diet. Against these findings is the work of Mackay (1933*a*) who, noting the fact that 'milk anaemia' in infants is similar to 'milk anaemia' in rats, was unable to obtain evidence that in the former copper is a deficiency as it would appear to be in rats. She concluded (Mackay, 1933*a*), that although copper deficiency may occur in isolated cases of nutritional anaemia, it plays no part in the great majority, though she admitted the possibility that the finding of many workers that iron alone is ineffectual may be due to the use of iron of absolute chemical purity, i.e. free from other heavy metals such as copper (Mackay, 1931). The iron preparation used in Mackay's (1933*a*) own series was not copper-free. Lottrup (1934) found copper to be ineffective in the treatment of anaemia in children, but quoted only two cases.

Usher, MacDermott, and Lozinski (1935) tested the efficacy of copper as a prophylactic agent against simple anaemia of infancy, making observations on 233 infants in an institution for foundlings. To one group they gave only iron, to a second copper and iron, and the third group was a control. They found that at the age of one year, the copper and iron group had a haemoglobin of 19 per cent. above that of the control group, while the group receiving iron alone had a haemoglobin of only 15 per cent. above the control. The copper also produced advantageous results by increasing the resistance to infections, and reducing the mortality rate, which was over 14.5 per cent. for the control children, 11.6 per cent. for those receiving iron only, and 6.3 per cent. for those given the additional copper. Muller (1935) stated that in mild and moderately severe anaemia in children he could obtain cure in three to four weeks with copper alone, but this finding is contrary to the results of all British and American workers. Görter (1931) brings forward some evidence regarding the action of copper from a different angle, finding that the copper content of the

blood in infants suffering from nutritional anaemia was twice as high as at birth, or as that found in control convalescent children. This he suggests may mean that the copper in the body has been mobilized in response to the need for haemoglobin; alternatively he admits that this finding may be interpreted as indicating that in those anaemias there is no shortage of copper. The same worker (Görter, 1933) has found a high percentage of copper in the blood in pregnancy and infectious diseases, suggesting that as both conditions necessitate increased production of haemoglobin there is in consequence a mobilization of copper.

These clinical researches into the function of copper as a haematopoietic factor have, as was also seen to be the case in animals, yielded conflicting results. It would appear probable, however, that copper in some form is necessary for normal erythropoiesis. Further research has been carried out with a view to determining at what stage copper acts in the process of maturation of the erythrocyte, and as to its mode of action.

#### *Mode of Action of Copper*

Elvehjem, Steenbock, and Hart (1929) have demonstrated that the haemoglobin of rat blood does not contain copper as part of its molecule. It has been further shown (Elvehjem, 1932; Elvehjem and Sherman, 1932) that although in rats the cure of anaemia was not produced by inorganic iron, these salts were readily assimilated and stored in the liver and spleen; if copper was subsequently given the iron in the liver was removed and built into haemoglobin. From these results Elvehjem concluded that copper does not function in the assimilation of iron, but plays a part in the conversion of the iron into forms which can be used for the construction of the haemoglobin molecule. Muntwyler and Hanzal (1933) also concluded that copper, when given to anaemic rats, can mobilize the iron stored in the liver to produce haemoglobin and increase the red-blood corpuscles. Parsons (1933) has pointed out that in nutritional anaemia of infancy, copper may in resistant cases build haemoglobin, but has no effect on the reticulocytes or the red-cell count, indicating that although copper can effect haemoglobin synthesis it has no effect on the 'stroma substances'. A similar conclusion was reached by Josephs (1932). These facts lead to the conclusion that copper speeds up a synthetic reaction already in progress, which is probably of a catalytic nature (Vaughan, 1936). Recognizing the fact that copper is active in combining with nitrogenous compounds, and that in haemocyanin, the blood pigment occurring in several invertebrates, copper takes the place of the haemoglobin molecule, the idea of copper acting as a catalyst seems a rational one (McGowan, 1930). Further, Cunningham (1931) has shown in the case of rats that copper definitely increases the proportion of 'organic' to total iron in the liver, and he considers that this change from 'inorganic' to 'organic' iron is probably a step in haemoglobin building dependent on the presence of copper. He

also suggests that any modification of the state of iron in this direction would probably be a change from 'inorganic' iron to an iron porphyrin and that it is possible that copper may promote this change. He makes an entirely speculative, but interesting, suggestion as to the process whereby copper may bring about the formation of an iron porphyrin. Turacin, the blood pigment of certain South African birds, is a naturally occurring copper porphyrin, and by chemical manipulation the copper can be displaced by iron, giving a compound practically indistinguishable from haematin. He suggests that the effect of copper in increasing the proportion of 'organic' iron is achieved by a preliminary formation of a copper porphyrin, and subsequent replacement of copper by iron. This would fit in with the observations outlined above and with the general chemical nature of the elements.

#### *Present Investigation*

The present series of researches was conducted in an effort to ascertain whether copper had any function in erythropoiesis in the human subject, and, if so, its mode of action. It has been shown in a previous paper (Hutchison, 1937) that pure inorganic iron alone is capable of curing the nutritional anaemia of infancy and childhood. Nevertheless, it was thought to be a reasonable assumption that if copper did play some part in haemoglobin synthesis, treatment by iron and copper would be more effective than by iron alone. In the iron deficiency anaemia of infancy at any rate, it would appear probable that the factors concerned in the production of iron deficiency, prominent amongst which are (1) low birth weight, (2) artificial feeding, and (3) delayed institution of mixed feeding (Fullerton, 1937; Neale and Hawksley, 1933; Mackay, 1931) are likely also to bring about the existence of a copper deficiency, bearing in mind the analogies existing in the distribution of iron and copper in tissues and food.

*Method of investigation.* Nine cases of nutritional anaemia in infancy and childhood have been studied. Iron and copper were used in the treatment of six of the cases in the following way. After four days on a diet of known iron content, inorganic iron as ferrous sulphate was given orally for periods of one to three weeks. This was then discontinued and the patients observed for varying periods until the haemoglobin values of the blood became constant, or showed no appreciable tendency to rise. Then copper, as cupric sulphate, was given orally and the effect on the haemoglobin recorded. The ferrous sulphate was given in doses of 4 or 8 gm. per week (equivalent to 803.5 or 1607 mg. of iron). It was dissolved in water with the addition of glucose to prevent oxidation (Parsons and Hawksley, 1933) and contained less than 0.0005 per cent. of copper. Copper sulphate ( $\text{CuSO}_4$ ) was given in doses of 40 mg. per week, save in one case where the dose was 30 mg. per week.

In the remaining three cases, ferrous sulphate was given in doses of

0.5 gm. per week for several weeks, in an attempt to produce an iron storage in the body without changing the haemoglobin level. This attempt was completely successful only in one case. In all three cases when the haemoglobin levels had remained constant for several weeks the iron medication was stopped for a variable time and then copper sulphate, in doses of 40 mg. per week, was given and any mobilization of the stored iron for haemoglobin formation calculated.

Weekly determinations of the haemoglobin and red cells were made in every case. The haemoglobin levels were determined by the Sahli method. The haemoglobinometer was standardized against blood whose iron content had been estimated, and it was found that a reading of 100 per cent. on the haemoglobinometer represented a haemoglobin content of 17.3 gm. per 100 c.c. of blood. The iron metabolism of each patient was demonstrated by a balance study (divided into seven-day periods) over the time during which iron was administered, and until a positive iron balance was re-established following discontinuance of the iron administration. In this way the amount of iron retained in the body was estimated, and the percentage of retained iron utilized for the formation of new haemoglobin calculated with a reasonable degree of accuracy. The iron content of the circulating haemoglobin was calculated by taking the blood-volume to be body-weight in kg. litres, and the iron content of haemoglobin to be 0.335

15

per cent. (Butterfield, 1909; Sachs, Levine, and Appelsis, 1933). The technique used in the conduction of these balance studies was described in a previous publication (Hutchison, 1937). The method used for determining the iron content of the faeces was described by Taylor and Brock (1934). The iron content of the urine was neglected, as all workers agree that urinary excretion of iron is negligible (Tompsett, 1934; Brock and Hunter, 1937).

#### Case Reports

*Case 1.* M. G., aged 1 year, 10 months. *Nutritional anaemia and upper respiratory infection.* This girl was admitted with severe nutritional anaemia (haemoglobin 31 per cent.); and an acute upper respiratory infection necessitated a transfusion of 80 c.c. citrated blood.

	Haemoglobin per cent.	Red-blood cells c.mm.	Colour index.
Before transfusion	31	—	—
After transfusion	37	3,760,000	0.49
One week later	34	3,860,000	0.44

Four days after the temperature had subsided, ferrous sulphate was commenced in doses of 8 gm. per week and continued for two weeks. An iron-balance study was conducted during the two weeks of iron therapy, and for two weeks after discontinuance of iron administration, by which time there was a positive iron-balance (Table I). It will be seen (Chart I) that during the two weeks of iron therapy and the week immediately

following, the haemoglobin level rose from 34 per cent. to 77 per cent. Throughout the next three weeks the haemoglobin rose from 77 only to 82 per cent. At this time copper was added to the diet as 40 mg. of cupric sulphate per week, and in this next week the haemoglobin rose from 82 per cent. to 95 per cent. Considered in terms of the iron added to the circulation, the effect of copper is more clearly demonstrated (Table I). During the four weeks of the metabolism study 1,493 mg. of iron were retained in the

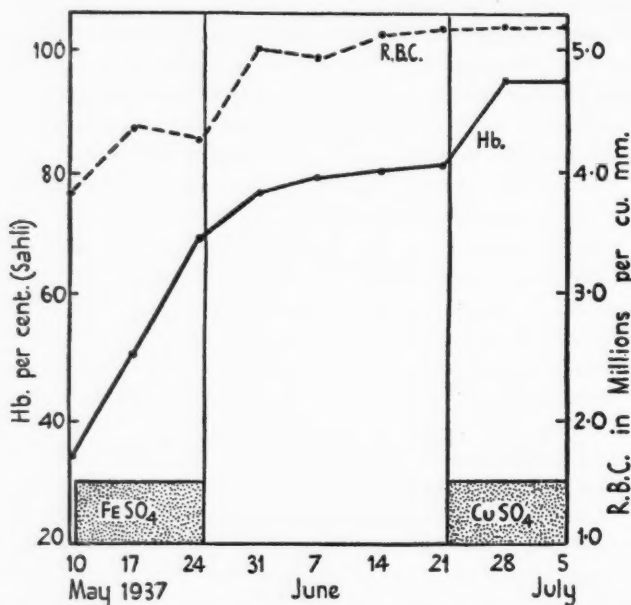


CHART I. Case 1. M. G., aged 1 year, 10 months. Nutritional anaemia. Treated by large doses of iron followed by copper.

body. Of this amount, during the two weeks of iron therapy and the week immediately following (which is included because of the 'lag effect' of the iron recently ingested) 87 mg. were utilized in haemoglobin synthesis, i.e. an average of 29 mg. per week. During the next three weeks, although there were 1,400 mg. of iron stored in the body, only 11 mg. went to the formation of haemoglobin, an average of 3.7 mg. per week. After the exhibition of copper, however, 26 mg. of iron were utilized in the next week.

Case 2. M. McC., aged 1 year, 7 months. Amentia and nutritional anaemia. This girl was admitted because of mental deficiency and nutritional anaemia. As in Case 1, treatment consisted first of iron and then of copper supplements to a diet of low iron-content. The dose of iron was 4 gm. of ferrous sulphate over a period of one week. Three weeks later she was given 40 mg. of copper sulphate for a further three weeks. An iron metabolism study was made from the commencement of treatment until two weeks after the cessation of iron therapy (Table II). The haemoglobin rose from the initial level of 47 per cent., before treatment was instituted, to 63 per cent. one week after the end of iron administration (Chart II). In the ensuing two weeks a further rise of only 4 per cent. occurred, but

following the addition of copper at this time, the haemoglobin level rose in the next two weeks, from 67 per cent. to 85 per cent., i.e. at a rate of 1.3 per cent. per diem. If now, the iron equivalents of these haemoglobin values are considered in relation to the total iron retention in the body (Table II) of 402 mg., as a result of the administration of 803 mg. of iron by mouth, it is found that during the week of iron therapy and the subsequent week, 44 mg. of iron (i.e. 10.9 per cent. of the total retention) were added to the

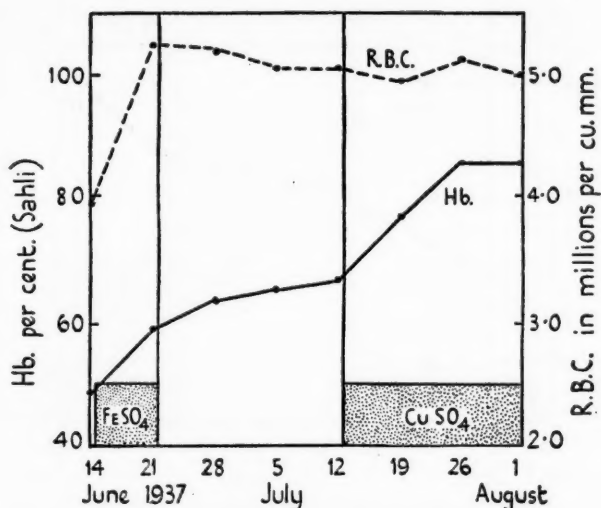


CHART II. Case 2. M. McC., aged 1 year, 7 months. *Amentia and Nutritional anaemia.* Treated by large doses of iron followed by copper.

circulation. During the next two weeks only 10 mg. of iron (i.e. 2.5 per cent. of the total retention) were utilized in haemoglobin building, but during the next two weeks following the start of copper therapy, the total haemoglobin iron rose by another 49 mg. (i.e. 12.2 per cent. of the total retention).

*Case 3. J. M., aged 1 year. Nutritional anaemia.* This patient was referred to hospital because of pallor. Examination of the blood showed a haemoglobin level of only 45 per cent. Four grammes of ferrous sulphate per week were given for two weeks. During this period and over the subsequent two weeks the iron balance was estimated. Three weeks after completion of the metabolism study, i.e. five weeks after the iron was discontinued, 40 mg. of copper sulphate per week were given for three weeks. The effect of treatment on the haemoglobin level is shown in Chart III and on the iron balance in Table III. The rise in the haemoglobin level from 45 per cent. to 69 per cent. one week after the end of iron treatment represented the addition of 73 mg. of iron to an 0.530 litre blood volume (24.3 mg. per week). The subsequent rise of 12 per cent. in the next four weeks to a haemoglobin level of 81 per cent. was equivalent to an increase in haemoglobin iron at the rate of 9.5 mg. per week. The administration of copper, however, was accompanied by a further increase of 53 mg. in the haemoglobin iron in two weeks, i.e. 26.5 mg. per week, which had

raised the haemoglobin level from 81 to 95 per cent. This figure is 10 per cent. above the 'normal' level of this age (Mackay, 1933 b). Furthermore, it is interesting to note that of the 733 mg. of iron retained by this infant as a result of iron treatment, only 22.4 per cent. was utilized in the formation of new haemoglobin, and 7.2 per cent. of the total retention was liberated for haemoglobin synthesis by copper.

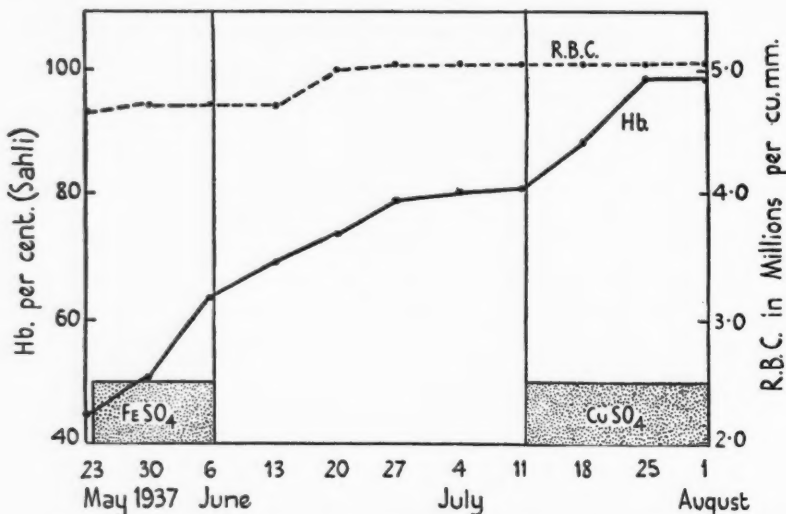


CHART III. Case 3. J. M., aged 1 year. Nutritional anaemia. Treated by large doses of iron followed by copper.

Case 4. H. C., aged 3 years, 3 months. Nutritional anaemia. Admitted to hospital because of failure to thrive and found to have a nutritional anaemia. The patient was placed on a diet of high caloric value with an iron-content of 23.3 mg. per week, and an iron metabolism study commenced immediately. One week later the administration of ferrous sulphate, in doses of 4 gm. per week, was begun and continued for three weeks. Unfortunately the metabolism study was discontinued three weeks after the completion of the iron course, and before a positive iron balance had been re-established (Table IV). This misfortune was due to the fact that the process of preparation of the faeces and determination of its iron content is of necessity a lengthy one, with the result that it is about three weeks from the end of any one weekly period before the iron retention during that period can be determined. From Chart IV it can be seen that over the period of iron therapy, the haemoglobin level rose from 40 per cent. to 66 per cent., i.e. 1.24 per cent. per diem. During the next week the haemoglobin rose to 71 per cent. due to a 'lag effect' of the iron, but during the next two weeks there was a haemoglobin rise of only 4 per cent., i.e. 0.29 per cent. per diem. Thereafter the child received 30 mg. of copper sulphate per week. During that period the haemoglobin level rose from 75 per cent. to 88 per cent., i.e. 0.93 per cent. per diem. As a result of the three weeks course of iron this child retained approximately 530 mg. of iron (Table IV). Of this amount 115 mg. were utilized for haemoglobin building during the iron course and the week thereafter, i.e. 28.8 mg. per week. During the next

two weeks the haemoglobin increase represented an iron utilization of only 7.5 mg. per week. The rise in the haemoglobin level from 75 to 88 per cent.

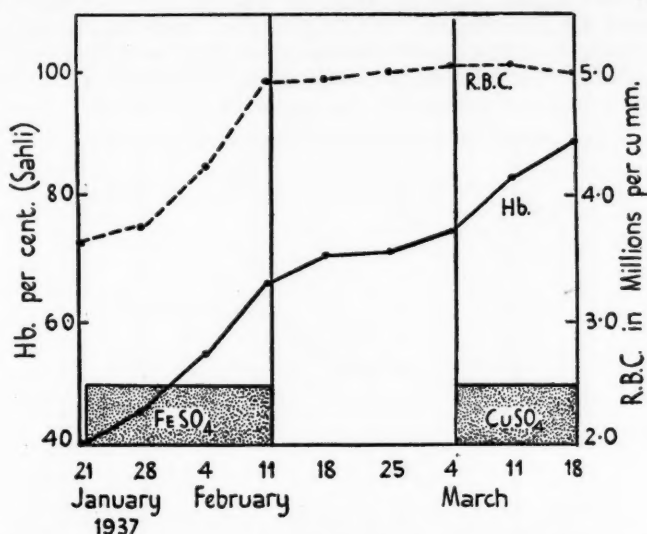


CHART IV. Case 4. H. C., aged 3 years, 3 months. Nutritional anaemia. Treated by large doses of iron followed by copper.

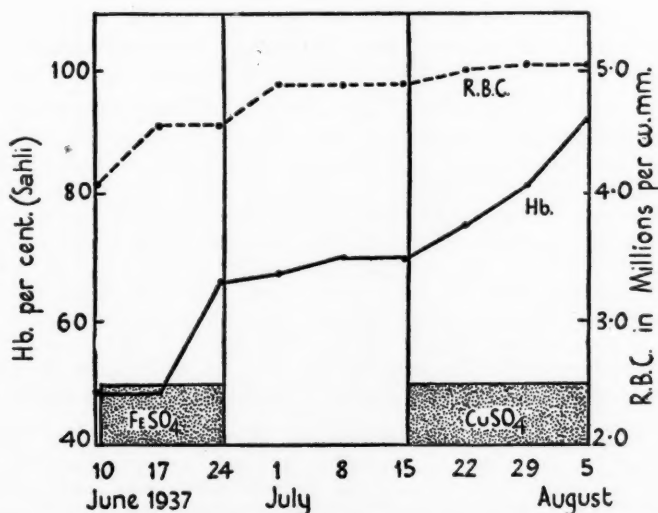


CHART V. Case 5. R. O'D., aged 10 months. Nutritional anaemia and rickets. Treated by large doses of iron followed by copper.

in the two weeks following the use of copper, however, represented the appropriation by the haematopoietic system of 46 mg. of iron, i.e. 23 mg. per week.

*Case 5.* R. O'D., aged 10 months. *Nutritional anaemia and rickets.* No vitamin D was administered until cure of the anaemia had been obtained with iron and copper in order that the haemoglobin response would be uninfluenced by other factors. An iron-balance study was instituted after four days on a fixed diet, and at the end of the first week treatment started with 4 gm. of ferrous sulphate per week, for two weeks. Three weeks later, a three-week course of copper (40 mg. per week) was given. As a result of

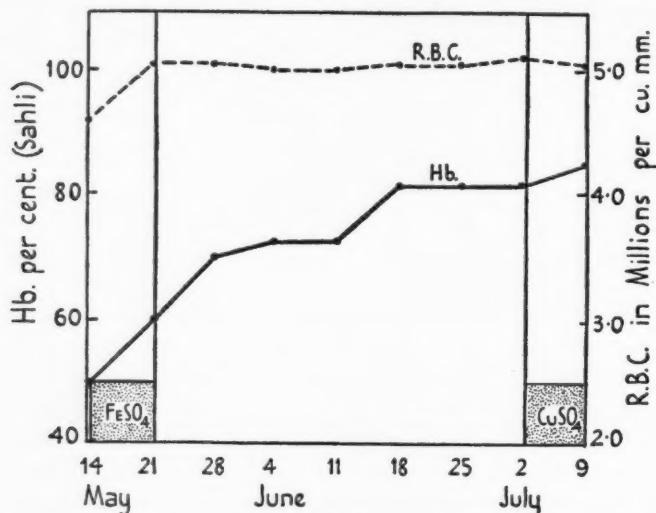


CHART VI. *Case 6.* M. G., aged 1 year, 10 months. *Nutritional anaemia.* Treated by large doses of iron followed by copper.

the iron therapy 720 mg. of iron were stored in the body (Table V). Sixty-three milligrammes of this amount were utilized for haemoglobin synthesis during the two weeks of iron administration (31.5 mg. per week), to produce a haemoglobin rise of 18 per cent. (1.29 per cent. per diem), (Chart V). During the next three weeks there was a rise of only 4 per cent. in the haemoglobin level, representing the utilization of 15 mg. of iron (5 mg. per week). Following the use of copper during the ensuing three weeks, the haemoglobin rose from 70 to 93 per cent. (1.10 per cent. per diem), necessitating the liberation of 79 mg. of iron from the storage depots, i.e. at the rate of 26.3 mg. per week. Thus of 157 mg. of iron transported from the storage depots to the bone-marrow for utilization in haemoglobin synthesis, over 50 per cent. was liberated as the result of the copper action.

*Case 6.* M. G., aged 1 year, 10 months. *Nutritional anaemia.* This girl, the twin of M. G. (Case 1) presented a much less profound degree of nutritional anaemia and in contrast to her sister was moderately well nourished. The mother insisted that the dietetic régime had been the same for both children from birth, and there had been no previous illnesses to explain the difference in their physical condition. As will be seen from Table VI and Chart VI this girl responded to treatment very differently from her twin. Eight grammes of ferrous sulphate were given over a period of seven days with retention of 589 mg. of iron. Thereafter no further iron was given. This was followed by a rise of haemoglobin from 50 per cent.

to 73 per cent. One week later, however, the haemoglobin level rose from 73 to 82 per cent. (1.29 per cent. per diem) in a period of seven days. A most careful inquiry into the dietetic and nursing régime failed to find an explanation for this occurrence. The haemoglobin level showed no further tendency to rise until the administration of 40 mg. of copper sulphate two weeks later, which caused a further rise of 3 per cent. during the next week.

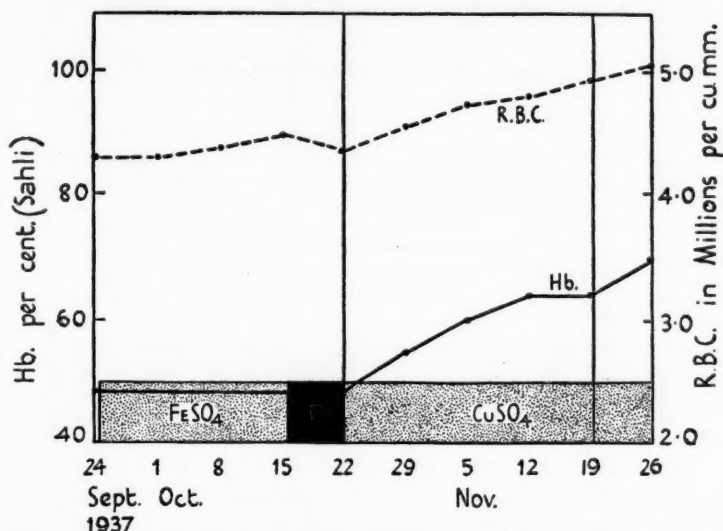


CHART VII. Case 7. H. C., aged 1 year, 4 months. Nutritional anaemia. Treated by small doses of iron followed by copper.

*Case 7. H. C., aged 1 year, 4 months. Nutritional anaemia.* Admitted with severe nutritional anaemia:—haemoglobin 48 per cent., red blood-cells 4,360,000 per c.mm. The administration of ferrous sulphate was started in doses of 0.5 gm. per week, and continued for three weeks. An iron-balance study during this period (Table VII) showed that the body retained 76 mg. of iron, and that a positive iron balance was present during the week immediately following the discontinuance of iron administration. The presence of this amount of iron in the body was not associated with any rise in the haemoglobin level (Chart VII). One week after discontinuance of iron administration, copper sulphate was given in doses amounting to 40 mg. per week, and three weeks later the haemoglobin level had risen by 15 per cent. to 63 per cent., a rise which necessitated the addition to the circulation of 56 mg. of iron, i.e. 73 per cent. of the total retention of 76 mg. No further rise in haemoglobin took place until the administration of iron in therapeutic doses caused a further rise to commence, the haemoglobin level ultimately reaching a normal level.

*Case 8. M. McL., aged 1 year, 3 months. Nutritional anaemia.* Ferrous sulphate (0.5 gm. per week) was administered to this case of nutritional anaemia (haemoglobin 55 per cent.) over a period of five weeks. The metabolism study was unfortunately stopped, probably one week before the iron balance would have become positive, following discontinuance of iron

administration (Table VIII). The difficulty of judging as to when to stop the collection and preparation of faeces was noted in Case 4. In contrast to the progress of events in the previous patient, this dosage of iron caused the haemoglobin level to rise from 55 per cent. to 72 per cent. in three weeks (Chart VIII), equivalent to the addition of 57 mg. of iron to the blood (Table VIII). Three weeks later, however, the haemoglobin level remained at 72 per cent., although there were still present in the body

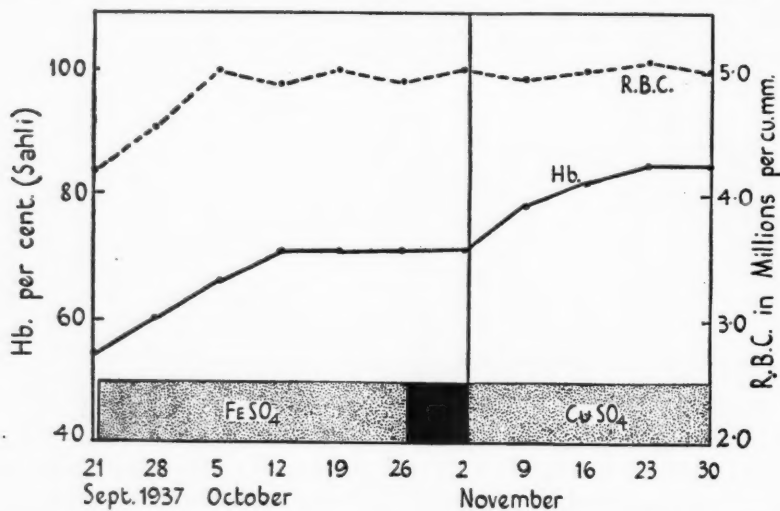


CHART VIII. Case 8. M. McL., aged 1 year, 3 months. Nutritional anaemia. Treated by small doses of iron followed by copper.

57 mg. of the total retention of 114 mg. of iron available for conversion into haemoglobin. Following the exhibition of copper at this time the haemoglobin level rose to 85 per cent. in the next three weeks (0.62 per cent. per diem) involving the utilization of 74 per cent. (42 mg.) of the 57 mg. of iron probably still stored in the body. It is of interest to note here that it is recognized to be more difficult to obtain a rise in the haemoglobin level when it approaches normal, than to effect the initial rise from the low level of the untreated anaemia. In this case the rise from 72 to 85 per cent. was effected by the administration of copper alone, after the cessation of a minimal iron dosage. The ability of copper to produce a high final haemoglobin level in some instances has been a notable feature in this series of cases.

Case 9. J. McF., aged 1 year, 2 months. Nutritional anaemia. In this patient, admitted with a fairly severe nutritional anaemia, copper failed to produce the desired satisfactory result. Ferrous sulphate was given, in doses amounting to 0.5 gm. per week, for three weeks. An iron-balance study of five weeks' duration (Table IX) revealed that the body had stored 58 mg. of iron as a result of iron administration, of which amount 13 mg. were utilized to produce a rise in the haemoglobin level from 52 to 56 per cent. (Chart IX). The administration of copper at this time was followed by the very small rise of 4 per cent. haemoglobin in the next two weeks, although there were still stored in the body 32 mg. of iron. Following the administration of therapeutic doses of iron, at this time, the haemoglobin

rose to 88 per cent. The irregularity of the response to this final iron therapy was, in part no doubt, due to the fact that this phase of the treatment was conducted at home, and coincided with the appearance of convulsions of unknown aetiology which the mother attributed to the medicine, the result being that the iron was not given with the desired regularity, nor in the prescribed amounts.

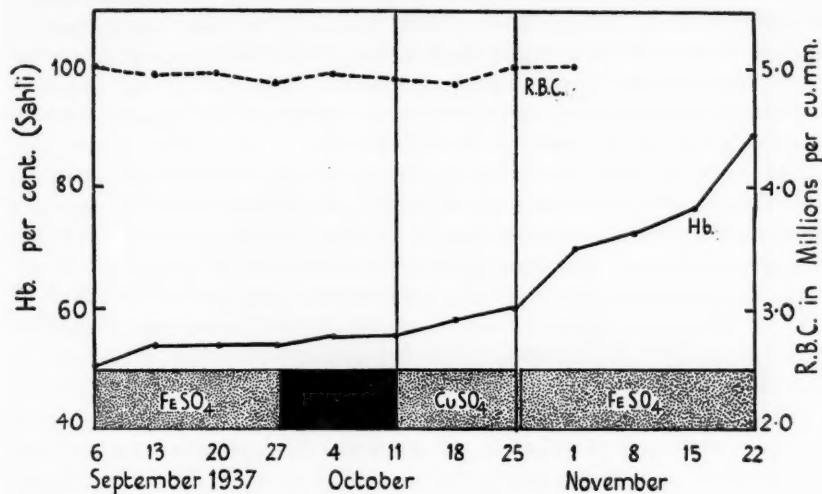


CHART IX. Case 9. J. McF., 1 year, 2 months. Nutritional anaemia. Treated by small doses of iron followed by copper.

### Discussion

The foregoing results confirm the finding (Hutchison, 1937; Brock, 1937; Fowler, and Barer, 1935, 1937; Widdowson, and McCance, 1937) that the body is capable of retaining large amounts of iron administered in the inorganic state, and that in anaemia only a small percentage of the total retention is available for haemoglobin synthesis. They further show that, on discontinuance of iron administration, although there is enough iron in the body to provide for several times the haemoglobin requirements, further utilization of this iron for those requirements does not take place to any marked extent. In Case 1, although after the haemoglobin level had risen from 34 to 77 per cent. there were still 1,400 mg. of iron available in the body, the haemoglobin level rose only a further 5 per cent. during the next three weeks. The administration of copper, however, caused an increase in the haemoglobin level of 13 per cent. in seven days. Similar results were obtained in Cases 2, 3, 4, and 5. Even in Case 6, although the haemoglobin response was for some reason inconsistent, copper produced a slight rise after the level had remained stationary for two weeks. A study of the results obtained in Cases 7, 8, and 9 reveals that the inefficacy of small

doses of iron (in contrast to the massive therapeutic doses) does not depend upon imperfect absorption from the gut. Thus in Case 7, although the small doses of iron failed to produce any change in the haemoglobin level, they did result in the retention of 76 mg. of iron, none of which was utilized for haemoglobin synthesis until the administration of copper was begun. These three cases therefore confirm a previous finding (Hutchison, 1937) that the necessity for large doses of iron does not lie in their ability to raise the iron content of the intestine above a certain 'threshold value', presumed to exist by some previous workers. In view of these results there can be little doubt that small amounts of copper are capable of causing a considerable increase in the rate of haemoglobin formation.

Regarding the mode of action of copper, as this element does not form part of the haemoglobin molecule (Elvehjem, Steenbock, and Hart, 1929), it does not combine with iron directly in forming haemoglobin. It would appear, therefore, to have a catalytic action, either by liberating more iron from the liver for the use of the bone-marrow (Muntwyler and Hanzal, 1933) or by converting iron, which is stored in the tissues, into a chemical form more suited for inclusion in the haemoglobin molecule (Elvehjem and Sherman, 1932; Cunningham, 1931).

A suggestion which does not clash with the facts already known, based on the preceding observations is put forward. That large amounts of iron are necessary to cure anaemia is well recognized (Heath, 1933; Witts, 1933), but it is not as yet fully understood why this should be the case. An explanation advanced by the present author (Hutchison, 1937) was to the effect that iron once absorbed and stored in the liver was no longer available for haemoglobin formation; and the suggestion was made that massive doses were required to overcome the rate at which iron could be stored in the liver, with the result that some iron would overflow into the blood-serum and thus be transported in an available form to the bone-marrow. Furthermore, it was noted (Hutchison, 1937) that there was apparently no tendency for iron, once stored in the tissues, to be re-excreted. Other workers attacking this problem from different aspects have tended to confirm these conclusions. McCance and Widdowson (1937) have pointed out that, in some way, iron must be transported very efficiently about the body, and showed that there was little evidence to suggest that the body ever excreted unwanted iron, either in the urine or faeces. Moore, Arrowsmith, and Quilligan (1937) have recently emphasized that there are two non-haemoglobinous forms of blood iron, (1) serum or plasma iron, (2) what they refer to as 'easily split-off' blood iron, the physiological functions of which have not been established. Further work (Moore, Doan, and Arrowsmith, 1937) has led them to believe that the plasma or serum iron is in fact iron which is being transported from the storage depots to the bone-marrow for utilization in haemoglobin formation.

Applying these facts to the present series, it is possible to advance a hypothesis regarding the mode of copper action which is in line with previous

work. The administration of iron produced a large iron-storage in the body. Of this store only a small amount went to haemoglobin formation, the remainder being apparently unavailable as the haemoglobin level ceased to rise appreciably (save in Case 6), until the administration of copper caused some of the stored iron to be liberated into the blood-stream for transportation to, and utilization by, the haematopoietic centres in the bone-marrow. The chemical nature of serum-iron is still obscure. That it is not in an inorganic state and is not dialysable is certain. It is probably trivalent and in organic combination, possibly as a complex ion (Moore, Doan, and Arrowsmith, 1937). Whether copper acts, as Cunningham (1931) suggests, by a preliminary formation in the liver of a copper porphyrin and by its subsequent replacement by iron must remain a matter for further research. There would appear to be little doubt, however, that copper plays an active part in the genesis of haemoglobin. If it be accepted that copper is not contained in the haemoglobin molecule, its action must be in the nature of a catalyst, and as the iron is probably mainly stored in the liver, it probably acts in that situation.

It would, therefore, seem wise in the case of the iron deficiency anaemias of infancy and childhood at any rate, to include some copper in all iron prescriptions. This would ensure that there was a sufficiency of serum-iron to meet the needs of the bone-marrow, by liberating iron from the liver into the blood-serum and would act as a supplement to that iron, which escaping the storage depots of the liver had already overflowed into the systemic circulation. Thus a maximum and most rapid haemoglobin response would be obtained in every case. This would be of advantage because of the marked susceptibility of those infants to infection, during which the administration of iron is ineffective (Mackay, 1931; Minot and Heath, 1932).

#### *Summary*

1. The literature regarding the role of copper in the iron-deficiency anaemias is reviewed.

2. Metabolism studies on nine infants revealed (a) that the administration of copper enhances the conversion into haemoglobin of iron stored in the tissues, (b) that iron given in doses so small as not materially to raise the haemoglobin content of the blood can, by subsequently giving copper, be mobilized and converted into haemoglobin.

3. It is suggested that copper acting as a catalytic agent enables iron to be converted into such a form that it can be transported by the blood-plasma from the storage depots to the bone-marrow where it can be utilized in the formation of haemoglobin.

This work was carried out during the tenure of a William McCunn Research Scholarship.

TABLE I

*The Action of Copper in the Treatment of Anaemia with Large Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	34	3,860,000	70	—
2	1630	514	1116	50	4,360,000	103	33
3	1635	1221	414	68	4,240,000	140	37
4	28	71	-43	77	5,000,000	157	17
5	28	23	+5	79	4,960,000	162	5
6	—	—	—	80	5,200,000	163	1
7	40 mg. CuSO <sub>4</sub> per week			82	5,200,000	168	5
8	—	—	—	95	5,200,000	194	26
9	—	—	—	95	5,200,000	194	Nil

Case 1. M. G., aged 1 year, 10 months. *Nutritional anaemia.* Weight 5.30 kg.  
 Blood volume =  $\frac{5.30}{15} = 0.353$  l.

TABLE II

*The Action of Copper in the Treatment of Anaemia with Large Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	47	3,960,000	127	—
2	823	370	453	59	5,280,000	160	33
3	19	86	-67	63	5,200,000	171	11
4	19	4	+15	65	5,040,000	175	4
5	40 mg. CuSO <sub>4</sub> per week			67	5,040,000	181	6
6	—	—	—	77	4,960,000	208	27
7	—	—	—	85	5,200,000	230	22
8	—	—	—	85	5,020,000	230	Nil

Case 2. M. McC., aged 1 year, 7 months. *Nutritional anaemia and amentia.*  
 Weight 7.0 kg. Blood volume =  $\frac{7.0}{15} = 0.467$  l.

TABLE III

*The Action of Copper in the Treatment of Anaemia with Large Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	45	4,710,000	138	—
2	832	431	401	51	4,960,000	156	18
3	832	440	392	64	4,880,000	197	41
4	28	88	-60	69	4,840,000	211	14
5	28	28	Nil	74	5,000,000	227	16
6	—	—	—	78	5,020,000	239	12
7	—	—	—	80	5,120,000	245	6
8	40 mg. CuSO <sub>4</sub> per week			81	5,200,000	249	4
9	—	—	—	88	5,200,000	270	21
10	—	—	—	98	5,240,000	302	32
11	—	—	—	98	5,124,000	302	Nil

Case 3. J. M., aged 1 year. *Nutritional anaemia.* Weight 7.93 kg. Blood volume =  $\frac{7.93}{15} = 0.53$  l.

TABLE IV

*The Action of Copper in the Treatment of Anaemia with Large Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	23	12	11	40	3,630,000	146	—
2	832	589	243	45	3,760,000	165	19
3	832	421	411	55	4,310,000	201	36
4	832	635	197	66	4,930,000	242	41
5	29	290	-261	71	4,950,000	261	19
6	29	57	-28	72	5,050,000	265	4
7	29	51	-22	75	5,100,000	276	11
	30 mg. CuSO <sub>4</sub> per week						
8	—	—	—	81	5,140,000	297	21
9	—	—	—	88	5,030,000	322	25

Case 4. H. C., aged 3 years, 3 months. *Nutritional anaemia.* Weight 9.49 kg.  
 Blood volume =  $\frac{9.49}{15} = 0.633$  l.

TABLE V

*The Action of Copper in the Treatment of Anaemia with Large Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	20	13	7	48	4,120,000	170	—
2	824	375	449	48	4,660,000	170	Nil
3	824	514	310	66	4,660,000	233	63
4	20	59	-39	68	4,960,000	242	9
5	20	20	Nil	70	4,980,000	248	6
6	40 mg. CuSO <sub>4</sub> per week			70	4,960,000	248	Nil
7	—	—	—	75	5,040,000	266	18
8	—	—	—	82	5,100,000	291	25
9	—	—	—	93	5,080,000	327	36

Case 5. R. O'D., aged 10 months. *Nutritional anaemia and rickets.* Weight 9.17 kg. Blood volume =  $\frac{9.17}{15} = 0.611$  l.

TABLE VI

*The Action of Copper in the Treatment of Anaemia with Large Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	50	4,640,000	187	—
2	1635	909	726	60	5,040,000	223	36
3	28	173	-145	70	5,040,000	259	36
4	28	20	+8	73	5,020,000	270	11
5	—	—	—	73	5,000,000	270	Nil
6	—	—	—	82	5,040,000	304	34
7	—	—	—	82	5,080,000	304	Nil
8	40 mg. CuSO <sub>4</sub> per week			82	5,260,000	304	Nil
9	—	—	—	85	5,080,000	315	11

Case 6. M. G., aged 1 year, 10 months. *Nutritional anaemia.* Weight 9.60 kg. Blood volume =  $\frac{9.60}{15} = 0.64$  l.

TABLE VII

*The Action of Copper in the Treatment of Anaemia with Small Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	48	4,360,000	181	—
2	129	110	19	48	4,320,000	181	Nil
3	129	121	8	48	4,430,000	181	Nil
4	129	87	42	48	4,530,000	181	Nil
5	28	20	8	48	4,380,000	181	Nil
	40 mg. CuSO <sub>4</sub> per week						
6	—	—	—	55	4,640,000	205	24
7	—	—	—	60	4,780,000	226	21
8	—	—	—	63	4,800,000	237	11
9	—	—	—	63	4,920,000	237	Nil
	4 gm. FeSO <sub>4</sub> , 40 mg. CuSO <sub>4</sub> per week						
10	—	—	—	70	5,040,000	263	26

Case 7. H. C., aged 1 year, 4 months. *Nutritional anaemia.* Weight 9.72 kg.

$$\text{Blood volume} = \frac{9.72}{15} = 0.65 \text{ l.}$$

TABLE VIII

*The Action of Copper in the Treatment of Anaemia with Small Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	55	4,200,000	181	—
2	129	51	78	60	4,600,000	198	17
3	129	107	22	67	5,020,000	222	24
4	129	91	38	72	4,980,000	238	16
5	129	149	—20	72	5,020,000	238	Nil
6	129	118	+11	72	4,960,000	238	Nil
*7	12	25	—13	72	5,040,000	238	Nil
	40 mg. CuSO <sub>4</sub> per week						
8	—	—	—	78	4,980,000	258	20
9	—	—	—	82	5,020,000	271	13
10	—	—	—	85	5,120,000	280	9
11	—	—	—	85	5,020,000	280	Nil

\* Only a three-day period owing to error in disposal of faeces.

Case 8. M. McL., aged 1 year, 3 months. *Nutritional anaemia.* Weight 8.56 kg.

$$\text{Blood volume} = \frac{8.56}{15} = 0.57 \text{ l.}$$

TABLE IX

*The Action of Copper in the Treatment of Anaemia with Small Doses of Iron.*

Week of Treatment.	Intake of Iron, in mg.	Output of Iron, in mg.	Retention of Iron, in mg.	Hb. %.	R.B.C. per c.mm.	Iron (mg.) as Hb.	Iron (mg.) retained as Hb.
1	—	—	—	52	5,020,000	169	
2	122	123	-1	54	4,960,000	174	5
3	122	59	+63	54	5,960,000	174	Nil
4	122	109	+13	54	4,720,000	174	Nil
5	21	45	-24	56	4,920,000	182	8
6	21	13	+8	56	4,800,000	182	Nil
	40 mg. CuSO <sub>4</sub> per week						
7	—	—	—	58	4,760,000	188	6
8	—	—	—	60	5,020,000	195	7
	4 gm. FeSO <sub>4</sub> per week						
9	—	—	—	70	5,040,000	227	32
10	—	—	—	72	—	235	8
11	—	—	—	76	—	246	11
12	—	—	—	88	—	285	39

Case 9. J. McF., aged 1 year, 2 months. Nutritional anaemia. Weight 8.44 kg.

$$\text{Blood volume} = \frac{8.44}{15} = 0.56 \text{ l.}$$

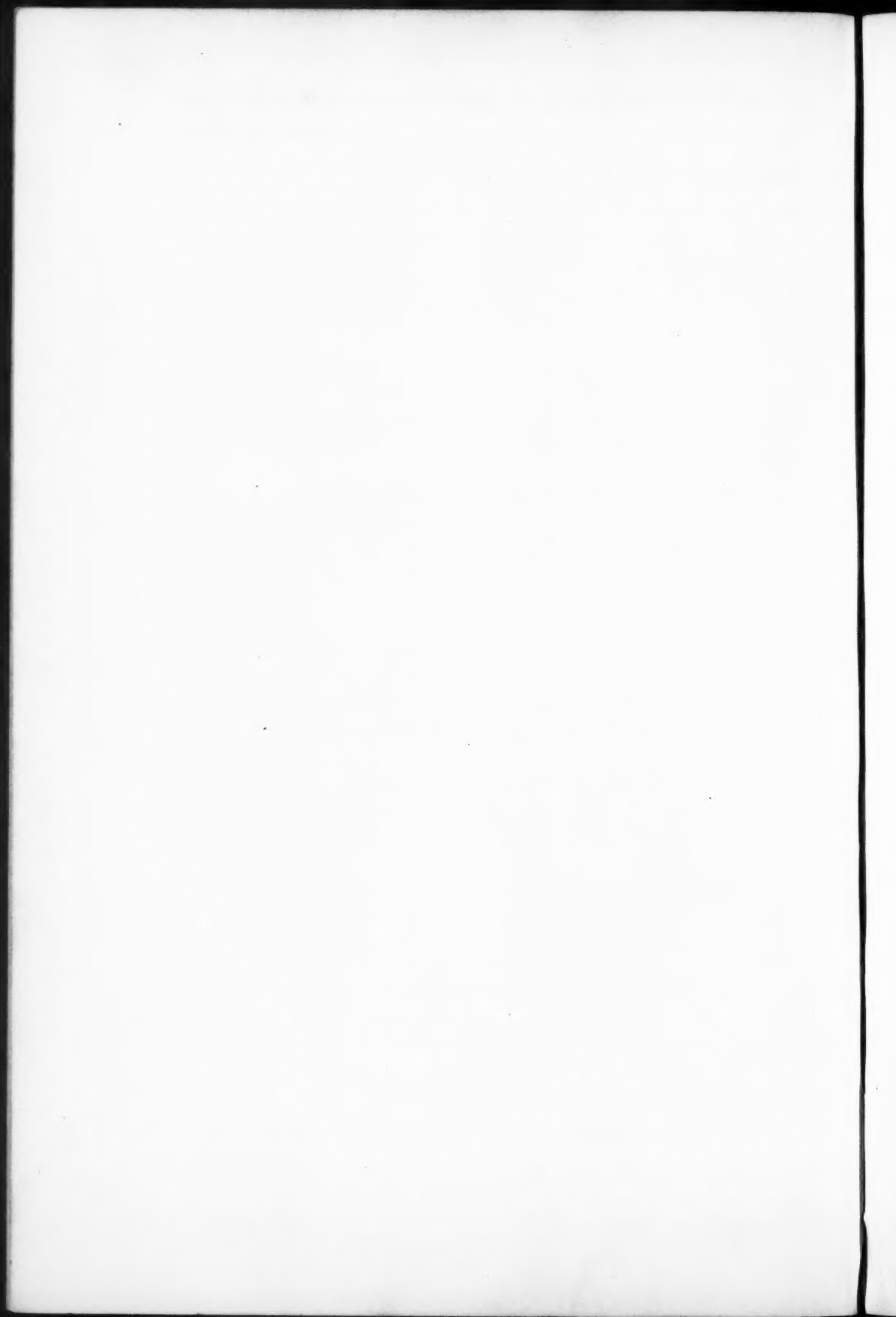
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THE ROLE OF COPPER IN IRON-DEFICIENCY ANAEMIA 419

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# DYSPNOEA: A REVIEW<sup>1</sup>

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## CONTENTS

INTRODUCTION . . . . .	422
DEFINITION . . . . .	422
THE CAUSES OF DYSPNOEA . . . . .	423
Physiological Considerations:	
(1) The Chemical Stimulus: (a) Anoxaemia; (b) Changes in Acidity.	
(2) The Reflex Stimuli: (a) From the Higher Centres; (b) The Hering-Breuer Reflex; (c) From the Carotid Sinus; (d) Other Stimuli; Summary.	
TYPES OF DYSPNOEA . . . . .	425
(1) Chemical Dyspnoea; (2) Reflex Dyspnoea; (3) Functional Dyspnoea.	
CONDITIONS COMMONLY ASSOCIATED WITH DYSPNOEA . . . . .	428
(1) Diseases of the Blood and Circulatory System:	
(a) Cardiac Dyspnoea; (b) Orthopnoea; (c) Cardiac Asthma; (d) Cheyne-Stokes Breathing; (e) Hypertension and Arteriosclerosis; (f) Anaemia.	
(2) Diseases of the Lungs and Pleura:	
(a) Lobar Pneumonia; (b) Broncho-pneumonia; (c) Chronic Infections of the Lung; (d) Bronchial Asthma and Tracheal Obstruction; (e) Emphysema; (f) Pneumoconiosis; (g) Pulmonary Atelectasis; (h) Neoplasms of the Lung and Mediastinum; (i) Pneumothorax; (j) Hydrothorax; (k) Thoracic Pain.	
(3) Disturbances of Metabolism:	
(a) Exercise; (b) Hyperthyroidism; (c) Diabetic Acidosis; (d) Nephritic Acidosis.	
(4) Disorders of the Nervous System:	
(a) Increased Intracranial Pressure; (b) Lesions near the Respiratory Centre; (c) The Anxiety Neuroses; (d) Hysterical Dyspnoea.	
(5) The Inhalation of Foreign Gases or Rarefied Air:	
(a) Poisonous Gases; (b) High Altitudes.	
SUMMARY . . . . .	448
REFERENCES . . . . .	448

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## INTRODUCTION

UNTIL the end of the last century it was the fashion to explain dyspnoea either on teleological grounds or on the basis of some mechanical impairment of the respiratory apparatus. With the development of the chemical study of the blood and the growth of knowledge of the chemical control of respiration, it became the vogue to explain all forms of dyspnoea in terms of acidosis or anoxaemia. During the past fifteen years it has become increasingly apparent that dyspnoea can seldom be explained on a chemical basis. The use of physiological methods in investigating the symptoms of disease has clearly shown that most cases of dyspnoea are reflex in origin rather than chemical. It might well be asked why there is little or no mention of this in most of the text-books of medicine or physiology. The first reason is that no general review of dyspnoea has been written since 1925 (Meakins and Davies, 1925; Means, 1924; Hofbauer, 1925). The second reason is that the physiologists have had the first (and often last) word in dictating the cause of dyspnoea to the clinicians. When the physiologists were interested in the chemical regulation of respiration they explained dyspnoea in terms of chemical changes in the blood. Now the carotid sinus occupies the stage, and it is interesting that carotid sinus reflexes occupy a prominent place in explanations of dyspnoea given in many of the recent text-books of physiology and applied physiology; and this with very inconclusive proof that the carotid sinus plays an important part in the normal regulation of respiration, and no proof of its significance in disease. There is a vast literature which might be quoted in any review of dyspnoea. Much of it is repetition. Where possible only the more recent contributions are referred to, and it can be assumed that these contain a full bibliography of earlier work.

## DEFINITION

In the minds of most clinicians the term dyspnoea is no more worthy of precise definition than 'headache' or 'cough.' Nevertheless many intricate definitions have been given. Most of them complicate rather than clarify the issue by a rigid exclusion of the use of the term in all cases where the subject is not conscious of respiratory distress. ('Dyspnoea is the consciousness of the necessity for increased respiratory effort' (Meakins and Davies, 1925). 'Dyspnoea is essentially a symptom, not a sign; the symptom that arises whenever, in carrying on the respiratory function difficulty is encountered' (Means, 1924). 'When the breathing enters consciousness unpleasantly and produces discomfort, it is called dyspnoea' (Wright, 1936). These definitions exclude the use of the word not only in comatose or anaesthetized subjects, but also in those whose threshold of sensitivity to distress of any kind is lowered by illness or constitutional factors. Not infrequently patients who exhibit obvious signs of respiratory embarrassment will refuse to admit the sensation of breathlessness (Goldscheider, 1932; Knipping, 1933). Even in

normal, healthy individuals it is impossible to define any particular respiratory rate or volume at which respiratory distress will occur (Richards, Cournand, and Rappaport, 1935; Deming and Hanner, 1936; Anthony, 1934). By adopting these rigid definitions the absurdity is admitted that the hysterical patient who shows no evidence of increased ventilation or respiratory embarrassment, but complains of inability to get enough air into the lungs, is truly dyspnoeic (Christie, 1935); while the patient with pneumonia who, though breathing rapidly with the physical signs of respiratory distress, refuses to admit a feeling of breathlessness, is not dyspnoeic. Fortunately, most clinicians are more concerned with the usefulness of the word dyspnoea in describing a significant clinical entity than in the text-book definition of the term. In this they are justified, since dyspnoea may be defined etymologically as difficult, painful, bad, or disordered breathing. The word can therefore be used objectively as well as subjectively, and the more elastic definition of dyspnoea as breathing associated with effort is fully justified. It must not be imagined that dyspnoea and hyperpnoea are synonymous. Hyperpnoea is increased ventilation of the lungs, and there may be no respiratory effort until ventilation is considerably augmented.

#### THE CAUSES OF DYSPNOEA

The immediate cause of respiratory effort must be stimulation of some part of the nervous mechanism which controls respiration. In defining the cause of dyspnoea in any individual it is therefore begging the question merely to describe the underlying morbid anatomy. To state that the dyspnoea of a massive pleural effusion is due to loss of functioning lung is just as inadequate as to state that the dyspnoea of uraemia is due to loss of functioning kidney. The mechanism by which the lesion affects the nervous control of respiration must also be defined. Such a differentiation between cause and effect is not only of theoretical interest, it is of fundamental importance in the treatment of dyspnoea. To define the cause of dyspnoea in these terms necessarily requires some knowledge of the physiology of respiration. Unfortunately the text-books of physiology are more devoted to describing the physiological principles involved than in emphasizing their relative importance. The essentials are obscured by a wealth of detail, and yet certain aspects of respiratory physiology which are of paramount importance for a proper conception of the mechanism of dyspnoea are not discussed. The nervous control of respiration must therefore be briefly considered, with particular emphasis on those aspects which have a bearing on dyspnoea.

#### *Physiological Considerations*

The maintenance of breathing depends on the rhythmic activity of the respiratory centre or centres. This rhythm, both with regard to the rate and depth of breathing, can be modified either by chemical changes in the centre itself, or by nervous stimuli acting on the centre.

(1) *The chemical stimulus* may be either lack of oxygen or changes in acidity of the respiratory centre.

(a) *Anoxaemia*. Until recently, moderate anoxaemia was believed to increase the irritability of the respiratory centre and thus produce rapid, shallow breathing and dyspnoea. More recent evidence has rendered this view untenable, and it is now believed that uncomplicated anoxaemia depresses the centre (Starling, 1936; Wright, 1936 *b*; Smyth, 1937). The relationship of anoxaemia to changes in respiration is discussed below (p. 426).

(b) *Changes in acidity*. The respiratory centre is extremely sensitive to changes in hydrogen-ion concentration. Any increase in acidity immediately results in stimulation of the centre to greater activity, respiration becomes deeper and faster, the increase in depth being the more characteristic. Conversely a decrease in acidity results in a diminution of the depth and rate of respiration.

(2) *The reflex stimuli* which may affect the respiratory centre fall into several groups.

(a) *Stimuli from the higher centres*. The respiratory system is unique in that though it is primarily one of the rhythmic involuntary processes, it is also very sensitive to voluntary control and to the emotions. Not only is the respiratory rhythm profoundly altered during talking, eating, laughing, crying, and various emotional states: even unemotional thought may be associated with gross respiratory irregularities (Golla and Antonovitch, 1929; Wittkower, 1934; Paterson, 1935). The importance of these reflexes will be further stressed when dealing with dyspnoea in the respiratory neuroses.

(b) *The Hering-Breuer reflex*. Since the early days of respiratory physiology it has been known that distension of the lungs caused a reflex inhibition of inspiration. The mechanism of this reflex is now well understood. When certain nerve-endings in the lung are stretched, impulses are sent through the vagus nerve to the respiratory centre, which inhibit inspiration. In other words, when the lung is inflated by the inspiratory act, these 'stretch receptors' in the lung prevent over-distension by discharging impulses which stop inspiration. The reflex thus controls respiratory depth. It also plays a part in the control of respiratory rate. When the reflex is abnormally stimulated respirations not only become more shallow, but they become more rapid. To appreciate the significance of this reflex in the production of rapid and shallow breathing and of dyspnoea, it is important to remember that it is the tension change, or stress in the lung, and not the volume change, which acts as the stimulus (Adrian, 1933; Haldane and Priestley, 1935). This brief description of the Hering-Breuer reflex represents the views now accepted by the large majority of physiologists. It is also claimed that the vagus contains fibres which slow respiration and others which inhibit the depth of expiration. The significance of these, either in health or disease, has not been established.

(c) *Stimuli from the carotid sinus*. Considerable confusion exists as to the physiological significance of the carotid sinus in the regulation of respiration.

The subject is reviewed in most of the text-books of physiology and is summarized by Haldane and Priestley (1935) as follows: 'On the whole it seems that the reflex control of the breathing by chemical stimulation of the carotid nerve-endings has not been established, at any rate as regards carbon dioxide. In respect of oxygen it has perhaps hardly been proved that the hyperpnoea of anoxaemia is a carotid reflex effect apart from changes in the circulation.' Even if it be true that chemical stimulation of the carotid sinus or carotid gland plays a part in the regulation of respiration, its importance cannot be great. The response to carbon dioxide that is claimed for the sinus merely reinforces the response of the respiratory centre itself. The response to anoxaemia that is claimed cannot be of importance in man, since even severe anoxaemia may not lead to any significant degree of hyperventilation (see pp. 426 and 447).

(d) *Other stimuli.* Afferent impulses from the skin, from the thoracic cage, and from other parts of the body have been shown to influence the respiratory rhythm under certain conditions (Harrison, Harrison, Calhoun, and Marsh, 1932; Harrison, 1935; Hess, 1931; Fleisch, 1934; Gesell and Moyer, 1935). There is no good evidence, however, that these reflexes play a significant part in the reflex control of respiration, and still less that they play a role in the production of dyspnoea.

#### *Summary.*

A satisfactory description of the cause of dyspnoea in any individual must include the mechanism by which the nervous control of respiration is impaired. Respiration is controlled by the chemical sensitivity of the respiratory centre, by reflexes arising in the lungs, and by stimuli from the higher centres. Many other reflexes which affect the respiratory rhythm have been described, but their significance, either in health or disease, has yet to be demonstrated. Dyspnoea may therefore be classified as follows:

(1) 'Chemical Dyspnoea', where the cause is a chemical change in the respiratory centre.

(2) 'Reflex Dyspnoea', where the cause is some exaggeration of the reflexes arising in the lungs.

(3) 'Functional Dyspnoea', where the cause is some exaggeration of the stimuli from the higher centres.

#### TYPES OF DYSPNOEA.

##### (1) *Chemical Dyspnoea.*

Until quite recently the dyspnoea of pneumonia, cardiac failure, and most other conditions associated with respiratory distress, was explained on the basis of either anoxaemia or increased acidity of the respiratory centre. Such an explanation has proved to be erroneous in most cases. (It will be seen from this review that pure chemical dyspnoea is a clinical rarity.

(a) *Oxygen lack (anoxia, or tissue anoxaemia).* It has already been stressed that anoxaemia depresses the respiratory centre. There remain two possible

mechanisms by which oxygen lack may stimulate the respiratory centre indirectly:

(i) The respiratory centre may be stimulated through the carotid sinus. The evidence that this may occur is inconclusive (see p. 424).

(ii) Oxygen is necessary for the oxidation and disposal of acid products of metabolism. It is therefore possible that, where there is oxygen deficiency, these acids might accumulate in the blood and thus stimulate the respiratory centre. If this occurs it should be possible to demonstrate an increase in the acidity of the blood. But in almost every condition associated with anoxaemia, such measurements of blood acidity have been made and, except where carbon dioxide elimination is also impaired, a change has been found to the alkaline side rather than to the acid. (See Cardiac dyspnoea (p. 428), Pneumonia (p. 439), High altitudes (p. 447)). There is no evidence that uncomplicated anoxaemia in man can lead to acid stimulation of the respiratory centre, except where death is imminent.

For many years it has been customary to explain most types of dyspnoea in disease on the basis of anoxaemia. That this should have been so is all the more remarkable since it has long been known that uncomplicated anoxaemia is not associated with dyspnoea. 'The relatively slight increase in the amount of air breathed during very serious anoxaemia has frequently been lost sight of in the interpretation of clinical symptoms. . . . In the very dangerous pure anoxaemia of high altitudes or carbon monoxide poisoning, increase in the breathing is not a prominent symptom' (Haldane and Priestley, 1935). A miner with carbon monoxide poisoning or a person at a very high altitude may lapse into coma without any suggestion of respiratory distress. In some cases there may be slight hyperventilation, but even this is often absent (see High altitudes, p. 447). The only conclusion that can be drawn from these straightforward observations is that anoxaemia does not cause dyspnoea. Remarkable as it may seem, we are faced with the paradox that although the physiologists have failed to prove any mechanism whereby anoxaemia can produce dyspnoea, and practical experience has shown that uncomplicated oxygen lack does not lead to shortness of breath, yet anoxaemia occupies a conspicuous place in the text-books as a cause of dyspnoea in disease. This is true of text-books of medicine as well as text-books of applied physiology. The conception which many clinicians have of the significance of anoxaemia in the production of dyspnoea is as dangerous as it is erroneous; dangerous because oxygen therapy is often withheld from patients sorely in need of it, either on account of the absence of dyspnoea, or because this form of therapy does not relieve the dyspnoea. Although lack of oxygen has little or no immediate effect on the respiratory rhythm, it must be remembered that the myocardium is particularly susceptible to anoxaemia. Where exposure to anoxaemia is prolonged, dyspnoea from heart failure may result. This is particularly true where the heart is damaged by disease or where it is strained by exercise. The evidence that anoxaemia may lead to myocardial damage is discussed in the section on high altitudes (p. 447).

(b) *Acidosis*. The effect on respiration of changes in the acidity of the blood or respiratory centre has already been described. There is no doubt that acidosis may result in hyperventilation through stimulation of the respiratory centre, and perhaps in lesser degree through stimulation of the carotid sinus. As will be discussed in their respective sections, there is no evidence that acidosis plays a significant rôle in the dyspnoea of the pneumonias or cardiac failure. Even in uraemia and exercise there are factors probably more important than changes in acidity which influence the respiratory rhythm. Only in the Kussmaul's breathing of diabetic acidosis, in the acid poisonings, and in emphysema can dyspnoea be truly ascribed to acidosis.

### (2) *Reflex Dyspnoea*

The manner in which the Hering-Breuer reflex responds to tension changes in the lung has already been described. There are two groups of pathological processes which may lead to changes in lung tension and which might therefore be associated with a disturbance of this reflex.

(a) In pulmonary atelectasis and some cases of pneumonia there is a shrinkage of one or more of the lobes of the lung so that the rest of the lung is 'put on the stretch.' In these circumstances, when there is increased tension in the walls of the alveoli and bronchi, it might be expected that the Hering-Breuer reflex would decrease the depth and increase the rate of respiration. Rapid and shallow breathing is characteristic of pulmonary atelectasis.

(b) In congestive heart failure and many inflammatory conditions of the lung the pulmonary capillaries are engorged with blood. Consequently the lungs become rigid and less distensible, so that a greater degree of traction has to be exerted to inflate them. In other words, any volume change in the lung will be associated with a tension change or stress on the alveolar walls, which will be greater than normal. It might be expected that in these circumstances the Hering-Breuer reflex would tend to make respiration more shallow and rapid. Rapid and shallow breathing is a characteristic of pulmonary congestion. The experimental and clinical evidence that the dyspnoea of these two groups is due to a local reflex arising in the lung, and the evidence that abnormal tension changes in the lung do occur, will be given when discussing the individual clinical entities. What evidence there is that dyspnoea may arise from stimulation of reflexes outside the lung will also be described. (See Pulmonary atelectasis (p. 443), Pneumonia (p. 439), Congestive heart failure (p. 428), &c.)

### (3) *Functional Dyspnoea (Neurotic Dyspnoea)*

Breathing is unique among the rhythmic involuntary processes in that it is very sensitive to voluntary control and to the emotions. It is hardly surprising therefore that the respiratory system is not uncommonly the seat of expression of psycho-neurotic symptoms. In both hysteria and the anxiety neuroses, dyspnoea is a frequent complaint. Respiratory distress associated

with mental stimuli is also not an uncommon sequel of encephalitis lethargica. (See *The respiratory neuroses*, p. 446.)

#### CONDITIONS COMMONLY ASSOCIATED WITH DYSPNOEA

A description of all the conditions with which dyspnoea may be associated would embrace a large part of the practice of medicine. Only the more common of these are dealt with. It may be assumed, however, that where dyspnoea occurs in diseases which are not discussed, the mechanism is similar to that described under some allied condition. An example of this is bronchiectasis, where the dyspnoea may be due to emphysema, or asthma, or a low grade broncho-pneumonia.

##### 1. *Diseases of the Blood and Circulatory System*

(a) *Cardiac dyspnoea.* 'The first indication of cardiac failure is to be found in a diminished tolerance of exercise. Of the very numerous tests of cardiac efficiency and inefficiency that have been devised, based as they are mainly upon pulse-rate or upon blood-pressure or upon both, there is none that approach in delicacy the symptom breathlessness' (Lewis, 1937). Since this represents the almost universal opinion of cardiologists, it is indeed remarkable that it is hard to find two text-books which agree on the cause of this breathlessness.

Cardiac dyspnoea has been variously ascribed to increased venous pressure, reduction in the vital capacity, a deficient interchange of gases in the lung, deficiency in blood-supply to the respiratory centre, an increase in the metabolic rate, pulmonary engorgement, and various reflex stimuli. From the available evidence it seems that there are two main causes of cardiac dyspnoea, the one chemical, the other reflex. Usually, if not invariably, the reflex cause is the more important.

The various theories will be discussed individually, the more probable being dealt with first.

(i) *Reflexes arising in the lung.* The mechanism by which pulmonary congestion may lead to reflex stimulation of the Hering-Breuer reflex, and consequently to dyspnoea, has already been briefly discussed (p. 427). In order to prove that cardiac dyspnoea may be due to such a reflex it is necessary to show (1) that pulmonary congestion causes reflex dyspnoea, (2) that pulmonary congestion is present in all cases of cardiac dyspnoea, and (3) that the degree of dyspnoea is proportional to the degree of pulmonary congestion. These criteria have been satisfied by experiments both on animals and on man.

Churchill and Cope (1929), and Harrison, Calhoun, Cullen, Wilkins, and Pilcher (1932), by isolating the vascular connexions of one lung in animals, were able to show that an increase in the capillary pressure of the lung is associated with rapid and shallow breathing. The absence of any chemical

changes in the blood and the disappearance of dyspnoea after vagal section showed that the rapid breathing is reflex in origin. Dunn (1920), Binger, Brow, and Branch (1924), Binger, Boyd, and Moore (1927) have shown that the production of multiple pulmonary emboli results in rapid and shallow breathing. They found that this rapid and shallow breathing disappears on vagal section and that it depends on pulmonary congestion rather than on chemical changes in the blood (Binger and Moore, 1927; Binger, Boyd, and Moore, 1927). Drinker, Peabody, and Blumgart (1922) showed that mechanically produced pulmonary congestion is associated with a decreased distensibility of the lung, and Partridge (1935) has found that under these conditions the electrical discharges concerned in the Hering-Breuer reflex are increased. These experiments suggest that, in animals, pulmonary congestion leads to an increased rigidity of the lung, which in turn leads to rapid and shallow breathing through stimulation of the Hering-Breuer reflex. *Good*

The evidence that pulmonary congestion in man may cause reflex dyspnoea is equally convincing. In 1891 von Basch described the rigidity ('Lungenstarre') of the lung in heart failure with congestion. He and his associates showed that at autopsy the lungs were less distensible than normally, and suggested that in this mechanical limitation of inspiration lay the cause of cardiac dyspnoea. This post-mortem change has been confirmed by many investigators, some of whom have suggested that, instead of a mechanical limitation of inspiration, some disturbance of the Hering-Breuer reflex is responsible for the respiratory embarrassment (Meakins and Davies, 1925; Hofbauer, 1925; Anthony, 1930; Fraser, 1927; Harrison, 1935). The inferences which have been drawn from post-mortem observations on the degree of distensibility of the lungs are open to question since van der Brugh (1900) and Christie and McIntosh (1934) have demonstrated that death results in a profound alteration of the elastic properties of the lung. However, Christie and Meakins (1934) have clearly shown that in the living subject pulmonary congestion is associated with a decreased distensibility of the lung. They did this by recording simultaneously the intrapleural pressure and the tidal air in man. The former is a direct measurement of the stress or tension of the lung, and the latter a measure of the degree of expansion. From these tracings an accurate analysis of the elastic properties of the lung could be made. It was found that the greater the degree of heart failure, the less distensible the lung became. Furthermore, clinical improvement was found to be associated not only with slowing and deepening of the respirations, but also with increased distensibility of the lung. They concluded that there was a direct relationship between pulmonary distensibility and dyspnoea in heart failure. Christie and Meakins also found that on deep inspiration the force exerted on the lung was perfectly normal, although the degree of distension was greatly reduced in cardiac failure. The diminution in vital capacity is thus due to increased rigidity of the lung rather than to any impairment of the muscles of inspiration. It seems fair, therefore, in patients with cardiac failure, to accept the vital capacity as a gauge of the rigidity of the lung. Numerous

observers have noticed the close parallelism between the degree of dyspnoea and the reduction of vital capacity (Harrison, 1935; Christie and Beams, 1923; Peabody, 1916; Pratt, 1922; Budelmann, 1934). This observation provides further evidence that dyspnoea is proportional to the degree of pulmonary congestion in heart failure. It might be said that a good clinician could have guessed this without the aid of measurements of pleural pressure or vital capacity. But it would only have been conjecture, as cardiac dyspnoea may occur with no physical signs of pulmonary engorgement. There is good evidence therefore that cardiac failure is associated with pulmonary congestion and that the increased rigidity of the lung causes reflex dyspnoea through stimulation of the vagus nerve.

(ii) *Chemical stimulation of the respiratory centre.* Anoxaemia as a possible cause of dyspnoea has already been discussed and discredited (p. 426). Furthermore there is no direct correlation between the degree of anoxaemia and the degree of dyspnoea in heart failure, and the relief of anoxaemia by oxygen therapy may not relieve dyspnoea (Harrison, 1935; Jansen, Knipping, and Stromberger, 1932; Fraser, 1927; Means, 1924; Richards and Barach, 1934.) (For other references see Meakins and Davies, 1925.) There may be more dyspnoea in a case of mitral stenosis with only slight cyanosis than in a case of morbus caeruleus. It must not be forgotten, however, that anoxaemia is particularly deleterious to the myocardium (p. 447), and may thus produce dyspnoea indirectly by increasing pulmonary congestion.

It has been claimed that cardiac dyspnoea is caused by increased acidity of the respiratory centre, due either to an impaired elimination of carbon dioxide in the lungs or to a sluggish circulation in the brain. There is no evidence, except in the very advanced stages of congestive heart failure, of any impairment of carbon dioxide elimination in the lungs. On the contrary there is ample evidence that carbon dioxide elimination is increased and that a slight but definite gaseous alkalosis results (Christie and Meakins, 1934; Harrison, 1935; Fraser, 1927). (For other references see Meakins and Davies, 1925, and Peters and van Slyke, 1931.) The absence of carbon dioxide retention, even in the presence of considerable anoxaemia may be explained on the basis of differences in the solubility and in the dissociation curves of oxygen and carbon dioxide. It is only in cases of 'extreme congestive failure' or of 'pulmonary disease in addition to heart failure' that there is any impairment of carbon dioxide elimination in the lungs (Fraser, 1927). Even in these cases respirations are rapid and shallow and not of the type associated with acidosis. There is therefore little justification for the widely expressed belief that pulmonary congestion causes breathlessness by decreasing the power of the lungs to aerate the blood passing through them.

The hypothesis that cardiac dyspnoea is due to a diminished blood-supply to the respiratory centre is part of the 'forward failure' theory of heart failure. 'Breathlessness is probably to be ascribed to a deficiency in the flow of aerated blood to the head and neck' (Lewis, 1937). The validity of this hypothesis depends on the assumption that the cardiac output is diminished

in heart failure. The literature on this question is voluminous and the reader is referred to reviews of the subject by Harrison (1935) and Fishberg (1937). The available evidence does suggest that usually, but not invariably, the cardiac output is subnormal in patients with heart disease. There is no constant relationship, however, between diminished cardiac output and the degree of dyspnoea. Furthermore, many procedures which increase the cardiac output (without a proportionate increase in the metabolic rate) are of no benefit in the relief of symptoms (Harrison, 1935), and in shock there is usually no evidence of dyspnoea. Finally, cardiac dyspnoea is usually associated with orthopnoea, and sitting up does not increase the cardiac output, but decreases it (p. 433).

There is another school which believes that abnormal metabolism is a factor in the production of cardiac dyspnoea. The basal metabolic rate is increased by 25-50 per cent. in heart failure (Peabody, Wentworth and Baker, 1917; Resnik and Friedman, 1935; Du Bois, 1924). There is, however, no evidence that this increase is due to anything more than the extra work performed by the muscles of respiration (Resnik and Friedman, 1935; Du Bois, 1924; Strieck and Marble, 1935). The increase in basal metabolic rate is the result and not the cause of cardiac dyspnoea. Similarly, increase in the oxygen debt on exercise (Eppinger, Kirsch, and Schwarz, 1927; Herbst, 1928; Meakins and Long, 1927) has probably nothing to do with the production of dyspnoea. The increase is inconstant (Harrison and Pilcher, 1930), and in any case could affect respiration only through the medium of chemical changes in the blood. The evidence against such chemical changes has already been discussed.

The evidence that cardiac dyspnoea may be due to chemical changes in the respiratory centre is thus extremely unconvincing. On the other hand, there is considerable evidence that no significant chemical changes occur. It can be concluded that, at the most, chemical changes in the respiratory centre play a very minor rôle in the production of cardiac dyspnoea, except perhaps in the terminal stages when death is imminent.

(iii) *Reflexes arising outside the lung.* The carotid sinus is frequently quoted as being in part responsible for cardiac dyspnoea (Wright, 1936; Fishberg, 1937). There is no evidence that this is so. These claims are based solely on the double assumption that chemical changes in the blood can produce dyspnoea through stimulation of the sinus and that cardiac dyspnoea is associated with chemical changes in the blood. Probably neither of these assumptions is true, and they have been criticized above.

Afferent impulses from the thoracic cage and from other parts of the body have been suggested as factors in the production of cardiac dyspnoea (Hess, 1931; Harrison, Harrison, Calhoun and Marsh, 1932; Fleisch, 1934; Harrison, 1935; Gesell and Moyer, 1935). The evidence that these reflexes are of significance in health is unconvincing. There is no evidence that they are of significance in disease.

(iv) *The vital capacity.* Decrease in vital capacity is often advanced as

one of the causes of cardiac dyspnoea. It is true that congestion and rigidity of the lungs lead to a diminution in the vital capacity which is usually proportionate to the degree of dyspnoea (p. 429), but this by no means indicates that the one is the cause of the other. Similar correlations can be established between dyspnoea and abnormalities of other sub-divisions of the volume of air in the lungs. For instance, the ratio of residual air (the amount of air in the lungs on full expiration) to total capacity (the amount of air in the lungs on full inspiration) is increased in direct proportion to the degree of dyspnoea (Binger, 1923; Meakins and Christie, 1929; Christie, 1932), and the reserve air is usually decreased (Hofbauer, 1925; Meakins and Christie, 1929). It is obvious that this does not mean that dyspnoea is due either to a relative increase of the residual air or to decrease of the reserve air. The only significance of these abnormalities is that they confirm the diminished distensibility of the lung in reflex dyspnoea.

(v) *Increased venous pressure.* Several investigators have shown that the venous pressure is usually raised in proportion to the degree of dyspnoea (Ernstene and Blumgart, 1930; Budelmann, 1934; Blumgart and Weiss, 1928; Allen and Hochrein, 1930; Harrison, 1935). It has been suggested that this increase in venous pressure impedes blood flow through the respiratory centre. But in carcinoma of the neck and mediastinum, and other conditions where the flow of blood to the superior vena cava is obstructed and the venous pressure in the veins from the head greatly elevated, there may be little or no evidence of dyspnoea. Furthermore, vascular stasis in the respiratory centre would lead to chemical dyspnoea, and there is no evidence that this occurs (p. 429). Respiratory reflexes arising in the right auricle have also been suggested, but there is no good evidence that such a reflex exists, either in health or disease. In all probability the correlation between venous pressure and dyspnoea is an indirect one—both bear a direct relationship to the pulmonary congestion of heart failure. There is no evidence that changes in venous pressure have any direct effect on respiration.

(vi) *Summary.* Cardiac dyspnoea is largely if not wholly due to the increased rigidity of the lung which follows pulmonary congestion. This pulmonary rigidity causes reflex dyspnoea through stimulation of the vagal nerve-endings in the lung. Except in the terminal stages of heart failure, it is improbable that an increase in the acidity of the respiratory centre is a factor in the production of cardiac dyspnoea. It is even more improbable that anoxaemia, raised metabolic rate, diminution in vital capacity, elevation of venous pressure, the carotid sinus, or other reflexes arising from without the lung, play any direct part in cardiac dyspnoea. It is well to emphasize, however, that anoxaemia and the raised metabolic rate may play an indirect part by their effects on the heart leading to increased pulmonary congestion.

(b) *Orthopnoea.* The term orthopnoea refers to dyspnoea which is relieved by assuming the upright position. It is often described as dyspnoea which is produced, or aggravated, by assuming the recumbent position. Although

*Anoxaemia acts on heart muscle & not on the*

the meaning of the two definitions is essentially the same, the latter is etymologically incorrect. As orthopnoea is usually associated with heart failure it will be described as a form of cardiac dyspnoea. (Orthopnoea occurring in asthma or other diseases of the lung is discussed elsewhere.)

Numerous theories have been advanced to explain this interesting and common form of dyspnoea, but most of them are mere conjecture, incapable of analysis or proof. The various theories naturally fall into two groups: those which suppose that the dyspnoea associated with orthopnoea is primarily chemical, and those which suppose it to be reflex.

(i) *Evidence that the dyspnoea of orthopnoea is chemical in origin.* Although the dyspnoea of orthopnoea is frequently claimed to be chemical in origin (Wright, 1936; Haldane and Priestley, 1935), it can immediately be stated that there is no good evidence for this assumption. One hypothesis states: 'With a failing respiratory centre and consequent abnormal shallowness of respiration, anoxaemia is the natural result of the recumbent position, and the prevention of this anoxaemia by keeping the patient in a sitting position becomes an important part of treatment unless the same object is attained by oxygen administration' (Haldane and Priestley, 1935). ~~This theory presupposes that the recumbent position leads to anoxaemia.~~ There is no evidence that it does, and Calhoun, Cullen, Harrison, Wilkins and Tims (1931) have shown that in patients with orthopnoea there is no significant change in the oxygen content of either the arterial blood or blood from the jugular vein on assuming the recumbent position. In our own experience we have not observed any significant relief of the dyspnoea associated with orthopnoea by oxygen therapy. (It is curious that there does not appear to be any evidence in the literature on this aspect of oxygen therapy.) There is thus no evidence that orthopnoea is linked with changes in anoxaemia. ~~Even if it were, there is no evidence that anoxaemia can cause dyspnoea~~ (p. 447). says who?

According to another hypothesis, orthopnoea is supposed to be related to a deficient blood-supply to the respiratory centre. The recumbent position is said to exaggerate this deficiency, and chemical dyspnoea to result from the accumulation of acid products of metabolism as well as anoxaemia of the centre (Eppinger, Laszlo and Schürmeyer, 1931). This hypothetical deficiency in blood-supply to the respiratory centre has never been demonstrated (p. 430). Even if there were such a deficiency, there is an overwhelming mass of evidence that in normal individuals and in those with heart failure the cardiac output is increased rather than decreased on assuming the recumbent position (Neilson, 1936; Gladstone, 1935; Donal, Gamble, and Shaw, 1934; Beilshowsky, 1932; Schneider and Crampton, 1934; Sweeney and Mayerson, 1937; McMichael, 1937). Similarly, the circulation velocity is increased on lying down (Bock, Dill and Edwards, 1930). It is clear therefore that the relief of dyspnoea in orthopnoea is not due to improved circulation in the respiratory centre resulting from increased cardiac output on assuming the erect position.

The pressure in the jugular veins is increased in most patients with

orthopnoea (Blumgart and Weiss, 1928; Allen and Hochrein, 1930; Harrison, 1935), and is greater when lying down than when sitting. It has been suggested by Ernstene and Blumgart (1930) that the dyspnoea in these cases is due to venous congestion of the respiratory centre with consequent anoxaemia and accumulation of acids. The recumbent position exaggerates this congestion by further increasing the venous pressure. Considerable doubt has been cast on this theory by Weiss and Robb (1933), and Harrison (1935), who have shown that in some cases of orthopnoea there is no demonstrable increase in venous pressure, and by Calhoun, Cullen, Harrison, Wilkins and Tims (1931), who have shown that there is no undue accumulation of carbon dioxide or lack of oxygen in the venous blood from the brain. Furthermore, there is no direct relationship between increased venous pressure and cardiac dyspnoea (p. 432). From these observations it can be concluded that there is no good evidence that the dyspnoea associated with orthopnoea is due to chemical changes in the respiratory centre.

(ii) *Evidence that the dyspnoea of orthopnoea is reflex in origin.* The dyspnoea associated with orthopnoea is essentially a form of cardiac dyspnoea, and cardiac dyspnoea has already been shown to be primarily, if not wholly, reflex in origin, the stimulus being pulmonary congestion. It might therefore be thought that the relief of this form of dyspnoea on sitting up is due in some way to the relief of pulmonary congestion. There is good evidence that this is so. Hill, in 1895, was apparently the first to suggest that in the upright position blood is drained from the lungs to the splanchnic and other areas. Such a redistribution of blood might be expected from the laws which are known to govern the flow of venous blood to the right heart (Eyster, 1929; Field and Bock, 1925; Dock, 1935). That a change of distribution does in fact occur is suggested by the experiments of Ude (1934), who demonstrated a shift in the centre of gravity with change in posture, and by the plethysmographic studies of Atzler and Herbst (1923). The question remains as to how significant this redistribution would be in relieving pulmonary congestion. Many investigators have demonstrated an increase in the vital capacity on sitting up (Calhoun, Cullen, Harrison, Wilkins and Tims, 1931; Hurtado and Fray, 1933; Wilson, 1927; Hamilton and Morgan, 1932; Christie and Beams, 1923; Bohr, 1907). The reasons for supposing that such a change represents a decrease in pulmonary congestion have already been discussed (p. 429). There is also good clinical evidence of a parallelism between orthopnoea and pulmonary congestion. 'In isolated left heart failure, in which there is pulmonary engorgement, but neither systemic venous engorgement nor fall in arterial pressure, there may be the most violent orthopnoea, for example during attacks of cardiac asthma. Such observations point immediately to pulmonary engorgement as a factor in the production of orthopnoea. This inference is supported by the frequent amelioration or relief of orthopnoea when right heart failure is superimposed on insufficiency of the left heart' (Fishberg, 1937).

The case for the reflex origin of orthopnoea can be stated as follows: Since

cardiac dyspnoea is largely, if not wholly, reflex in origin, and since the stimuli which cause cardiac dyspnoea arise from congestion of the lung, orthopnoea might be expected to be due to changes in pulmonary congestion with changes in posture. There is a considerable evidence that engorgement of the lungs is in fact diminished on sitting up. There is no evidence that orthopnoea is associated with chemical changes in the blood, or with reflexes arising elsewhere than in the lung.

← (c) *Cardiac asthma.* (Paroxysmal cardiac dyspnoea, renal asthma.)

The essential nature of so-called 'cardiac asthma' is a matter for conjecture, although the clinical picture is well defined—'The term cardiac asthma is used to indicate a special form of severe paroxysmal breathlessness occurring chiefly at night. . . . The severer attack wakes the patient and brings him at once to a sitting position with a sense of intense suffocation. The breathing is increased in rate and becomes more and more forceful; he clutches surrounding objects and brings all the accessory muscles into play. But the chest, increasing in size, moves less and less effectively. Distress is terrible. Little air can be taken into the lungs and expiration is prolonged and powerful. Cyanosis comes and quickly deepens, while at first the veins remain unengorged. Pallor may be added. Sweat breaks out and is profuse. The man is brought within a short time into the throes of a fierce struggle for breath. The chest is filled with sibilant rhonchi and râles. The patient becomes semi-conscious. The attack begins to subside. In this, and sometimes in the milder attack cough develops and the patient brings up a little frothy and usually blood-stained sputum. He is left exhausted. Such a severe attack may last half-an-hour, an hour, or more. It threatens life, ending occasionally in fatal oedema of the lungs. In the early stages the pulse is quick (up to 120), and strong, and the systolic blood pressure is found to have risen; it is the rule for pressures to be high in the attack. In the later stages pressure may fall and the pulse become almost imperceptible' (Lewis, 1937).

There can be no question that cardiac asthma is associated with intense congestion of the lungs. The physical signs of rapidly increasing pulmonary engorgement during the attacks are both constant and definite (McGinn and White, 1934; Lewis, 1937; Fishberg, 1937; White, 1937). It is hardly necessary to discuss the additional evidence of laboratory measurements. The mechanism by which pulmonary congestion produces reflex dyspnoea has already been discussed, and the dyspnoea of cardiac asthma may be explained on the basis of reflexes arising in the lung due to pulmonary engorgement (p. 428). Why pulmonary engorgement should occur during sleep in these patients is somewhat of a mystery, although several theories have been advanced. There is always clinical evidence of strain on the left ventricle due to hypertension or some other cause, and the onset of pulmonary congestion is usually ascribed to failure of the left heart to expel the volume of blood it is receiving from the right heart. This does not explain the rather extraordinary fact that these attacks occur during absolute rest and are not

precipitated by exertion. Several explanations have been given. Eppinger, von Papp and Schwarz (1924) believe that a precipitating factor is increased venous return to the heart due to peripheral vasodilation, while Wassermann (1934) believes that reflexes from the carotid sinus are responsible. A sudden increase in sensitivity of the nervous system when the patient has been awakened by cough or dreams has been invoked by Harrison (1935), and others. Volhard (1931), Brunn (1928), and Gollwitzer-Meier (1931) have suggested an increase in the blood-volume due to resorption of oedema fluid during sleep. There is no direct evidence in favour of any of these hypotheses, and although there may be little evidence against them, the onus of proof is surely on those who propound the theories. On sounder ground is the possibility that the recumbent position during sleep favours pulmonary congestion, just as it does in orthopnoea. It is a common clinical observation that if the patient slides down in bed, an attack of cardiac asthma is more likely to occur; but as Fishberg (1937) has pointed out, this can only be a factor of secondary importance, since the patient may be able to assume the recumbent position while awake, with no ill effects.

Weiss and Robb (1933) have pointed out that the venules, as well as the arterioles, are sensitive to the liberation of adrenalin and cholin derivatives. They make the reasonable suggestion that excitement, or anything that induces autonomic activity during sleep, may result in a simultaneous elevation of the arterial pressure and constriction of small venules. Such a synchronism would mean not only that the left ventricle had to work against increased resistance, but that more blood was delivered to the lungs by the right ventricle. Under these conditions the exact balance between the outputs of the left and right ventricles might well be upset with consequent engorgement of the pulmonary circulation.

Another possibility, which we have not seen described, but which is based partly at least on fact rather than on fancy, is as follows:—With the onset of sleep and abolition of muscular movement, venous stagnation in the greater circulation is favoured. This is so both in health and disease. Consequently any sudden movement or stretching of the extremities in bed should cause a considerable influx of blood to the right auricle. That this sudden influx of blood to the right auricle may occur was suggested to us from the continuous records of the heart-rate, taken throughout the night on normal individuals. Boas and Goldschmidt (1932) and others have shown that movements during sleep usually cause an acceleration of the heart-rate, amounting to 10–20 beats per minute. These are average figures and the acceleration may be greater. In some of our cases the rate increased from a resting level of 60 beats per minute to 90 or 100 per minute, the whole period of acceleration lasting from 20 to 50 heart beats. Similar movements made when awake have little effect on the heart-rate. This phenomenon might be explained in several ways, but the most probable appears to be that after a period of complete muscular relaxation there may be considerable stagnation of blood in the veins. Any movement might then cause a sudden influx of blood to

the right heart. In patients with circulatory embarrassment and venous stasis this influx might be even greater than in the normal individual, and might well be sufficient to overload an already embarrassed left ventricle. While awake, and during restless sleep, frequent muscular movements prevent any accumulation of blood in the veins and ensure a more constant flow to the right auricle.

From this rather confusing array of theories it seems that the most probable explanation of cardiac asthma is as follows. The dyspnoea itself is reflex in nature, due to the rapid onset of pulmonary congestion. There are probably several factors involved in the production of this sudden pulmonary engorgement. While asleep the patient assumes a more recumbent position than usual, so that pulmonary congestion is favoured, the mechanism of this being the same as in orthopnoea. Due to a sudden muscular movement or stretching of the extremities while asleep, there may be an influx of blood to the right auricle from the peripheral veins. The right ventricle has no difficulty in increasing its output, but the left ventricle, already hovering on the brink of failure, is unable to cope with the sudden influx of blood. With more blood being expelled from the right ventricle than the left, pulmonary congestion is bound to occur. It is generally agreed that once the attack has started, a vicious circle is established. The increased respiratory effort facilitates the return flow of blood to the right heart, and at the same time the early onset of anoxaemia increases the incapacity of the left ventricle to expel the blood it is receiving. Pulmonary congestion is thus maintained.

*What does  
Harrison  
say to this?*

*good*

One other factor should be mentioned. As the term cardiac asthma would suggest, respirations are sometimes so wheezy and laboured as to simulate bronchial asthma, and in some cases the clinical picture suggests some degree of broncho-spasm. The sibilant rhonchi, the inspiratory position of the chest with low diaphragm, and the retraction of the intercostal spaces during inspiration (Weiss and Robb, 1933; Lewis, 1937; Fishberg, 1937) all suggest broncho-spasm; in fact, it is difficult to conceive what else could cause them. It is therefore probable that broncho-spasm is of considerable importance in increasing the severity of the dyspnoea. By its mechanical hindrance to respiration, ventilation is impaired, and anoxaemia and carbon dioxide retention result. The former provides further embarrassment to the heart and the latter chemically stimulates the respiratory centre. The cause of the broncho-spasm is unknown. It may be due to an overflow of vagal stimuli from the fibres concerned with the Hering-Breuer reflex, but this is only conjecture.

Why the attack ever passes off is also a mystery. It may be that a rapidly failing left ventricle and increasing anoxaemia in the tissues lead to a general vasodilatation. Blood would thus be transferred from the pulmonary to the systemic vascular bed, with consequent relief of pulmonary congestion. That this does indeed happen is suggested by the close resemblance that the termination of these attacks bears to shock. The

blood-pressure falls, the pulse is often imperceptible, and the deep cyanosis may change to a dusky grey.

It must be emphasized that any description of the mechanism of cardiac asthma is based on indirect evidence. There can be no excuse for dogmatism, and it is very probable that factors other than those which have been described are of considerable importance.

(d) *Cheyne-Stokes breathing.* This type of breathing was well known to Hippocrates, and yet its cause is still not understood. Periods of apnoea alternate with periods when the respirations progressively increase in amplitude, and eventually the subject may become intensely dyspnoeic. Respirations then progressively diminish in amplitude and another period of apnoea ensues. Cheyne-Stokes breathing may occur in cardio-renal disease, cardiac failure, cerebral haemorrhage, or any condition associated with anoxaemia or increased intracranial tension. Anoxaemia of the respiratory centre is generally held to be its cause. The exponents of this theory give convincing evidence that with deficiency of oxygen, the sensitivity of the respiratory centre is altered, so that its spontaneous rhythmic activity ceases. With cessation of respiration, carbon dioxide and lactic acid accumulate in the respiratory centre until the stimulus becomes so strong that the activity of the centre is reawakened. The excess of carbon dioxide is then removed, and the centre once more lapses into inactivity.

This explanation is probably correct in those cases where Cheyne-Stokes breathing is associated with a marked deficiency in the aeration of the blood. There is, however, an increasing weight of evidence that in cardiovascular disease and in conditions associated with increased intracranial tension the cause is more complex. It is not within the scope of this review to discuss the voluminous literature on the subject. The changes in arterial pressure, venous pressure, spinal fluid pressure, blood gases, and respiratory exchange, and the reactions to various therapeutic procedures, have been analysed in great detail. It is apparent from these observations that the periodic breathing of cardiovascular disease is different from that occurring with anoxaemia or intracerebral lesions. It is remarkable that this differentiation has not been stressed in the literature, as even the respiratory irregularity differs considerably in the two groups. In the cardiovascular group the cycle is of two to three minutes duration, and there is a perfectly regular fluctuation in the level at which the patient breathes. From what is known of the factors which control the respiratory level, this fluctuation must mean a periodic change in pulmonary congestion. In periodic breathing caused by anoxaemia or change in intracranial tension, the picture is entirely different. Only from four to five breaths may appear in each group of respirations. The regular waxing and waning of the regulations may be absent, and there is little or no change in the respiratory level (Biot's breathing).

(e) *Hypertension and arteriosclerosis.* Dyspnoea in these conditions may be due to a variety of causes. It may be associated with cardiac failure or with

emphysema; it may take the form of Cheyne-Stokes breathing or cardiac asthma. The mechanism of these types of dyspnoea has been described elsewhere. Another form described in hypertensive patients is the so-called paroxysmal or cerebral dyspnoea. The cause is said to be spasm of the cerebral arterioles. The blood-supply to the respiratory centre is thought to be impaired, so that anoxaemia and acidosis of the centre develop and the subject hyperventilates with intense dyspnoea (Volhard, 1931). These attacks differ in no way from cardiac asthma (p. 435). In view of the frequency of this condition in patients with hypertension, this would appear to be the more likely explanation.

(f) *Anaemia*. In severe anaemia there may be dyspnoea on the mildest exertion. In these cases the oxygen-carrying power of the blood is so reduced that the tissues may suffer from extreme lack of oxygen. The cause of this dyspnoea on exertion is presumably similar to that described below in the section on high altitudes.

## 2. Diseases of the Lungs and Pleura

(a) *Lobar pneumonia*. There is little agreement in the standard text-books as to the cause of dyspnoea in lobar pneumonia. 'Anoxia may be present from the vicious action of the toxin on the respiratory centre causing shallow breathing' (Wright, 1936). 'Many factors combine to produce the shortness of breath, pain, toxæmia, fever, anoxaemia, acidosis possibly, and loss of function in a considerable area of the lung' (Osler and McCrae, 1935). 'Pleuritic pain, by restricting the respiratory excursions, may result in this type of breathing. In many other instances it appears to be of a reflex nature resulting from the inflammatory process, which, through a reduction in the distensibility of the pulmonary tissue, exalts the sensitivity of the afferent vagal endings in the alveolar walls' (Best and Taylor, 1937). Other quotations could be given, but these will suffice to show the divergence of of opinion that exists.

*Evidence that the dyspnoea is of chemical origin*. Although there is ample evidence that lobar pneumonia is usually associated with anoxaemia, there is none that either acidosis or oxygen-lack are factors in the production of dyspnoea. Except perhaps in the terminal stages of pneumonia, there is an alkalosis rather than acidosis (Binger, Hastings and Sendroy, 1927). (For other references see Meakins and Davies, 1925.) With regard to oxygen-lack, there is little evidence of any parallelism between anoxaemia and the degree of dyspnoea. It is true that cyanosis usually increases with the severity of the disease, but the oxygen saturation seldom falls below 80 per cent., even when there is intense dyspnoea (Meakins and Davies, 1925). (For other references see Peters and Van Slyke, 1931.) Reports on the effect of oxygen therapy are usually difficult to interpret as details of changes in respiratory rhythm are seldom given. There is no good evidence that the

administration of oxygen relieves dyspnoea in lobar pneumonia. Patients with pneumonia are very susceptible to suggestion. We have seen subjective relief of dyspnoea in over 50 per cent. of cases by placing patients in a body plethysmograph, and suggesting symptomatic improvement. Slight subjective relief is therefore of little significance. When the respiratory rhythm, as well as the state of the arterial blood is carefully observed, the relief of anoxaemia is often found to have little or no effect on respiration. From a wide experience of oxygen therapy in the oxygen chamber of the Rockefeller Institute in New York, Binger and his co-workers state: 'We have frequently observed patients with pneumonia continuing to breathe at the rate of 40 or more to the minute even after the oxygen want has been relieved by oxygen administration. The occasional persistence of rapid respiration after crisis, when pulse and temperature have returned to normal, has suggested that the stimulus for accelerated respirations may be a local one resulting from the pulmonary lesion' (Binger, Boyd and Moore, 1927). Our own experience, and that of many others, has been similar (Lundsgaard, 1924; Binger and Davies, 1928; Binger, 1928).

The action of toxins on the respiratory centre as a cause of dyspnoea need not be considered very seriously. In pneumococcal empyema and other pneumococcal infections outside the lung, there may be no dyspnoea when the lung is not involved. The injection of toxins into animals does not stimulate the respiratory centre.

*Evidence that the dyspnoea is reflex in origin.* The evidence that generalized pulmonary congestion due to many different causes can produce reflex dyspnoea has already been discussed (p. 428), but in pneumonia there is no evidence that generalized congestion of the lungs occurs. With the recent popularity of pneumothorax in the treatment of pneumonia, there is ample data available on the pleural pressures of these cases (Blake, Howard and Hull, 1936; Lindskog, Harper and Friedman, 1936). It is apparent that the pleural pressure fluctuation with inspiration and expiration is not increased in lobar pneumonia. The lungs as a whole are therefore no more rigid than in normal individuals. Congestion and rigidity are confined to the infected lobes. The only question that need be discussed, therefore, is whether local congestion can produce reflex dyspnoea in the same way as does generalized congestion. The evidence on this question is scanty. From what is known of the physiology of the Hering-Breuer reflex, there is no reason why the stimulation of the nerve-endings in parts of the lung should not affect the respiratory rhythm. Porter and Newburgh (1916, 1917) have shown that the dyspnoea of experimental pneumonia is abolished by blocking or cutting the vagus nerves. Just what is the stimulus that augments the activity of the vagal nerve-endings in the lung in pneumonia is somewhat of a mystery. At first sight it might seem that local rigidity would act in the same way as generalized rigidity of the lung. Such a supposition does not bear close scrutiny. The inflamed and rigid lobe is subjected to just the same stress on inspiration as the other healthy lobes (Christie and McIntosh,

1934). Measurements of the intrapleural pressure in lobar pneumonia have shown that the lungs as a whole are not unduly rigid. There is therefore no evidence that the diseased areas are abnormally stretched on inspiration, even though they are congested.

*Summary.* There is good evidence that the dyspnoea of lobar pneumonia is reflex in origin, and none that it is caused by chemical changes in the blood or respiratory centre. The reflex stimulus probably arises in the vagal nerve-endings in the lung. Although the nature of this abnormal stimulus has not been established, it is presumably associated with the engorgement and rigidity of the inflamed lobes. When anoxaemia is sufficiently severe to embarrass the heart, generalized pulmonary congestion may add the factors which produce cardiac dyspnoea (p. 428). In other cases the picture may be complicated by the pain of pleurisy (p. 444).

(b) *Broncho-pneumonia.* There is no evidence that the cause of dyspnoea in broncho-pneumonia differs from that in lobar pneumonia.

(c) *Chronic infections of the lung.* Although dyspnoea may occur, it is seldom a prominent feature of chronic infections of the lung. Numerous investigators have claimed characteristic changes in the blood gases in pulmonary tuberculosis, but more recent studies indicate that, except in tuberculous pneumonia or in the terminal stages of the disease, these are absent (Varela, Recarte, and Esculies, 1930; Willenweber, and Lorenz, 1932; Cobet and Apitz, 1933). Where dyspnoea occurs, it is presumably due either to the same factors as in pneumonia or to the co-existence of emphysema or heart failure.

(d) *Bronchial asthma and tracheal obstruction.* The literature on the effects of respiratory resistance is voluminous, presumably on account of the ease of experimental approach and of interest in gas masks. The dyspnoea of asthma and tracheal obstruction is characteristic. If severe, it is associated with orthopnoea and with rather deep laboured respiration. Details of the respiratory changes need not concern us. Suffice it to say that respirations are usually prolonged. When obstruction is extreme, respirations may become rapid and shallow. The explanation usually given for the intense respiratory distress is impairment of aeration of the blood with consequent chemical stimulation of the respiratory centre. There is no doubt that in severe attacks of asthma both anoxaemia and carbon dioxide retention occur, and in these cases chemical stimulation of the respiratory centre may be of great importance (Meakins and Davies, 1925; Moore and Binger, 1927; Eloesser, 1931; Killick, 1935). Evidence has been accumulating, however, that in many cases the explanation is not so simple. Nissen and Cokkalis (1925), Morawitz and Siebeck (1909), and others, have observed that in experimental respiratory obstruction dyspnoea occurred before chemical changes in the blood had had time to affect the respiratory centre. Meakins and Davies (1925) describe cases of asthma with no retention of carbon dioxide. Nissen and Cokkalis (1925), Tiitso (1935), and others, have shown

that the response to respiratory resistance is quite different after vagotomy; the respiratory depth is decreased and the rate increased. In the case of resistance to inspiration the picture may be further complicated by the advent of pulmonary congestion and consequent rapid and shallow breathing (Moore and Binger, 1927).

The only conclusions that can be drawn from this confusing array of evidence are: (a) the most important cause of dyspnoea in asthma or tracheal obstruction is probably insufficient aeration of the blood, with chemical stimulation of the respiratory centre; (b) there is some evidence that vagal impulses from the lung may contribute to the increase in respiratory effort. The stimulus for this may be the stress on the alveolar walls consequent upon the greatly increased pressure fluctuation within the alveoli.

The cause of orthopnoea in these cases appears to be a fairly simple one. The resistance to the passage of air to and from the lungs is so great that the intrinsic muscles of respiration are unable to expand the lung, and elastic recoil is insufficient to deflate it. The accessory muscles of respiration are therefore brought into play, and the use of these is facilitated by the upright position.

(e) *Emphysema of the lung.* Dyspnoea is the earliest and most common symptom of emphysema. Over a period of months or years the patient complains of increasing breathlessness on exertion. As the lesion progresses, even the exertion of coughing may produce attacks of dyspnoea sufficiently severe to simulate asthma. In the later stages, when signs of circulatory impairment have supervened, dyspnoea at rest and orthopnoea may appear.

Aeration of the blood as it passes through the lungs is grossly deficient in emphysema, and there can be little doubt that the dyspnoea is due in large part to the retention of carbon dioxide and acid stimulation of the respiratory centre. It is not within the scope of this review to analyse the factors which impair haemo-respiratory exchange in emphysema. These have been fully discussed in several recent publications (Christie, 1934; Kountz and Alexander, 1934; Hurtado, Kaltreider and McCann, 1935; Sonne, 1934; Christie, 1937). The chronicity of the disease allows the patient with emphysema full scope for chemical compensatory changes in the blood. The inability to eliminate carbon dioxide is efficiently compensated by an increase in the bicarbonate reserve (carbon dioxide combining power). This compensatory mechanism is sufficient to ensure a normal acidity of the blood while the patient is resting, but any increase in metabolism, such as occurs during exercise or during a violent attack of coughing, is immediately associated with an increase in the blood carbon dioxide and stimulation of the respiratory centre. Increased ventilation is called for, but the subject with emphysema is unable for purely mechanical reasons to increase ventilation. The chest is already in the inspiratory position and the diaphragm so low that expansion of the lungs can be accomplished only with the aid of the accessory muscles (Christie, 1934, 1937; Kountz and Alexander, 1934; Best

and Taylor, 1937). Expiration can also be performed only by means of an unnatural muscular effort. Owing to loss of pulmonary elasticity, the lung can no longer deflate by a passive process of elastic recoil. The air must be squeezed out of the lungs—a definite muscular act performed for the most part by the accessory respiratory muscles. This impairment of respiratory mechanics also accounts for the inability to respond to the inhalation of carbon dioxide by the normal degree of hyperventilation (Meakins and Davies, 1925; Kountz and Alexander, 1934; Christie, 1934). The patient with emphysema is unable to hyperventilate.

The emphysematous patient is indeed in an unfortunate position. Both inspiration and expiration have to be executed by unnatural respiratory efforts, and a considerable proportion of the air which is inspired is wasted by not coming into proper contact with the pulmonary blood. At rest the patient can just make ends meet. With the help of compensatory changes in the blood, carbon dioxide elimination and oxygen absorption keep up with metabolic demands. When the metabolic demands are increased by exercise, this balance breaks down. Carbon dioxide accumulates in the blood and anoxaemia increases, so that true chemical dyspnoea due to acid stimulation of the respiratory centre appears. In the later stages, when signs of circulatory impairment have supervened, cardiac dyspnoea and orthopnoea may appear. In some cases the picture is further complicated by broncho-spasm (Christie, 1937; Kountz and Alexander, 1934).

(f) *Pneumoconiosis*. Pneumoconiosis may be associated with dyspnoea. What evidence is available suggests that the functional impairment in pneumoconiosis is of the same nature as in emphysema (Kaltreider and McCann, 1937; Hurtado, Fray and McCann, 1933).

(g) *Pulmonary atelectasis* (massive collapse of the lung). After massive collapse of one or more lobes, there is clear-cut evidence that the lung is under increased tension, due to shrinkage of the lobe or lobes involved. X-ray evidence of displacement of the thoracic contents towards the site of collapse suggests that this is so, and measurements of the intrapleural pressures prove that it is so. Intrapleural pressures as low as  $-43$  cm. of water on inspiration and  $-33$  cm. of water on expiration have been described (Elkin, 1927; Habliston, 1928; Blake, Howard, and Hull, 1936). This can only mean that the uncollapsed lobes are greatly overstretched. It might be expected, therefore, that the stretch receptors in the lung would be stimulated to decrease the depth and increase the rate of respiration (p. 424). Rapid and shallow breathing is characteristic of atelectasis, and Moore (1927) and others have shown that this is indeed due to vagal reflexes arising in the lung. The chemical changes in the blood that may occur after atelectasis are transitory and bear no relationship to the dyspnoea (Andrews, 1925).

(h) *Neoplasm of the lung and mediastinum*. Dyspnoea, either at rest or on exercise, is a frequent symptom of intrathoracic neoplasm. In some cases

the dyspnoea is associated with inspiratory stridor, and in these there is compression of the trachea. Aeration of the blood is impaired and chemical dyspnoea results in the same way as in asthma (p. 441). In others there is no respiratory obstruction, and no correlation can be established between dyspnoea and the extent of lung involved (Maxwell and Nicholson, 1930). We know of no investigations of respiratory function in this type of case. The dyspnoea may be associated with orthopnoea, and there is frequently no evidence of anoxaemia. It can only be supposed that in these cases the cause is reflex rather than chemical; it could, for instance, be due to pressure on the pulmonary veins leading to pulmonary congestion.

(i) *Pneumothorax*. Where portions of the lung are collapsed by pneumothorax, dyspnoea may result. Diminution in the amount of functioning lung is commonly given as the explanation. To be of significance such a diminution must involve an impairment of aeration of the blood. Numerous investigators have analysed the arterial blood after therapeutic artificial pneumothorax, and it can be stated with assurance that in man no significant anoxaemia or carbon dioxide retention results from this procedure (Christie and McIntosh, 1936; Richards, Riley, and Hiscock, 1932; Hilton, 1933; Courmand, Bryan, and Richards, 1935). It is only after a very large and sudden pneumothorax that there is any impairment of haemo-respiratory exchange, and even this is transient.

There is convincing evidence that pneumothorax is associated with generalized pulmonary congestion. Christie (1936) has shown that after the induction of pneumothorax there is a proportionate increase in the rigidity of the lung due to increase in pulmonary congestion. With an extensive bilateral pneumothorax the change is comparable to that found in congestive heart failure. In all probability, therefore, the dyspnoea which may occur after pneumothorax is due to pulmonary congestion, the mechanism being similar to that in cardiac dyspnoea.

(j) *Hydrothorax*. The mechanism of dyspnoea in hydrothorax is presumably similar to that in pneumothorax.

(k) *Thoracic pain*. Pain on breathing, due to pleurisy or any other cause, is usually associated with a voluntary effort to decrease the depth of inspiration. Breathing becomes a conscious effort, and there may be considerable respiratory distress. Whether this effort to limit the depth of inspiration can be called true dyspnoea is open to question.

### 3. Disturbances of Metabolism

(a) *Exercise*. Several comprehensive reviews of the physiology of muscular exercise have recently been written (Bainbridge, 1931; Eggleton, 1936). As the subject is of greater interest to the physiologist than to the clinician, the question of the cause of dyspnoea on exercise will not be discussed in

detail. Though there is some evidence to the contrary, it is probably due in part to increased acidity of the respiratory centre from the products of increased metabolism. Various reflex stimuli may be of considerable importance, but the nature of these has not been established.

(b) *Hyperthyroidism*. In hyperthyroidism the basal metabolic rate is increased. Any further increase in the metabolic rate by even mild exercise will bring the hyperthyroid subject into the category of a normal individual indulging in more strenuous exercise. Dyspnoea on mild exertion is therefore characteristic of hyperthyroidism. When there are cardiac complications, the factors described under cardiac dyspnoea are, of course, superimposed.

(c) *Diabetic acidosis*. The essential stimulus is increased acidity of the respiratory centre due to the acid products of morbid metabolism. Respirations are, therefore, full and deep (Best and Taylor, 1937; Wright, 1936; Peters and Van Slyke, 1931). It should be emphasized that hyperpnoea rather than dyspnoea is characteristic of diabetic acidosis.

(d) *Nephritic acidosis*. Dyspnoea is a common symptom in the terminal stages of nephritis. The cause is usually described as acidosis, but, even where dyspnoea is extreme, breathing is seldom comparable to the 'air hunger' of diabetes. It is true that there is often a real acidosis, but this is usually complicated by the presence of heart failure (Fishberg, 1931). Dyspnoea in these cases is due to pulmonary congestion rather than to chemical changes in the blood. The generalization can be made that slight hyperpnoea is characteristic of nephritic acidosis, but where true dyspnoea intervenes cardiac failure should be suspected.

#### 4. Disorders of the Nervous System

(a) *Increased intracranial pressure*. Increase in the intracranial tension is not uncommonly associated with dyspnoea. This may either be in the form of Cheyne-Stokes breathing or of continuous dyspnoea. The cause is not wholly understood and there are probably two factors, either of which may predominate. The respiratory centre may be stimulated by pressure, or the diminution in the circulation through the medulla may provide a chemical stimulus. The literature on this subject is diffuse and inconclusive. No real contribution to our knowledge of the effect of intracranial pressure on respirations appear to have been made since the excellent review of the subject by Eyster (1906).

(b) *Lesions near the respiratory centre*. In cerebral tumours, encephalitis lethargica, and cerebral vascular lesions, the respiratory centre or the subsidiary centres between the medulla and pons may be involved. Various respiratory irregularities have been described which may or may not amount to dyspnoea. The mechanism involved is not understood. Paralysis of 'inhibiting centres', or stimulation of the respiratory centre due to

pressure of the tumour, have been suggested as the cause. In the post-encephalitic respiratory disorders there may be a large psychological element.

(c) *The anxiety neuroses.* In the anxiety neuroses and effort syndrome dyspnoea on mild exertion is a characteristic symptom. If the respirations are carefully observed or measured, they will be found to be somewhat irregular and shallow. Owing to the associated tachycardia, thoracic pain, sweating and nervousness, the dyspnoea is often ascribed to cardiac or thyroid disease. The respiratory irregularities are, however, characteristic and bear only a superficial resemblance to the rapid and shallow breathing of reflex dyspnoea. There is an extreme irregularity in the depth of respiration as well as in the level at which the patient breathes. A tracing of respirations on a recording spirometer almost invariably shows these characteristic abnormalities (Christie, 1935).

Increased irritability of the respiratory centre (Haldane and Priestley, 1935) and chemical changes in the blood (Lewis, 1918) have been suggested as the cause of dyspnoea in these cases. The close relationship between the emotions and the respiratory rhythm has already been stressed, and it is more probable that the dyspnoea is due to stimuli arising in the higher centres (Christie, 1935; Lewis, 1938).

(d) *Hysterical dyspnoea.* Hysterical dyspnoea is a fairly common clinical entity. It is usually described by the patient as a feeling of suffocation, or of inability to get enough air into the lungs. In its early stages this form of dyspnoea manifests itself in deep sighing respirations which interrupt the ordinary rhythm of breathing (Christie, 1935; White, 1937; Baker, 1934). It is a matter of opinion whether or not these sighing respirations can be said to constitute true dyspnoea. Less commonly the air hunger may lead to a paroxysm of hyperventilation, respirations being deep and laboured. The paroxysm usually follows some emotional stimulus and may persist until signs of tetany appear, so-called 'hyperventilation tetany'. The tetany is the result of true alkalosis due to loss of carbon dioxide in the expired air (Meakins, 1930; McCance, 1932; Scott and Cantor, 1933; Christie, 1935).

##### 5. *The Inhalation of Foreign Gases or Rarefied Air*

###### (a) *Poisonous Gases*

(1) *Inert gases.* The inhalation of pure methane or any other physiologically inert gas results in almost immediate unconsciousness. When diluted with air the effect will depend on the degree of dilution. The symptoms are similar to those observed at high altitudes (Haldane and Priestley, 1935).

(2) *Carbon monoxide.* The peculiar affinity of carbon monoxide for haemoglobin puts this gas in a category by itself. By combining with haemoglobin the carbon monoxide so impairs the oxygen-carrying power of the blood

that the tissues may be reduced to extreme degrees of oxygen want. The respiratory symptoms are similar to those observed at high altitudes. The absence of dyspnoea until dangerous degrees of poisoning have been reached has already been emphasized (Haldane and Priestley, 1935).

(3) *Gas warfare.* Dyspnoea is a prominent symptom after exposure to either the phosgene or chlorine group of 'lung irritant gases', or to mustard gas in sufficient concentration. Most of the English and French text-books on gas warfare suggest that dyspnoea is wholly or largely due to the combination of anoxaemia and carbon dioxide retention (Henderson and Haggard, 1927; Hederer and Istin, 1935; *Official History of the War*, 1923). The Germans have seen good cause to doubt this. In 1921 and 1925 comprehensive reviews of the work done on gas warfare by German physiologists and pathologists during the Great War were published (Laqueur and Magnus, 1921; Flury, 1925). Amongst other interesting observations on the functional impairment which follows gas poisoning, the absence of carbon dioxide retention, except in the terminal asphyxial stages, was demonstrated. Even when severe dyspnoea was present, the carbon dioxide in the arterial blood was usually below normal. Furthermore, it was shown that the lungs became more rigid and less distensible as the symptoms of phosgene poisoning developed, owing to congestion and oedema. They also showed that the dyspnoea could be abolished by blocking the vagus nerves. These observations bring the dyspnoea of phosgene poisoning into the same category as the dyspnoea of pulmonary congestion (p. 428). The cause is reflex and not chemical, the stimulus being increased rigidity of the lungs (Christie, 1937).

#### (b) *High Altitudes*

Anoxaemia is often invoked as the cause of dyspnoea in disease. The respiratory response to residence at high altitudes, the most simple form of anoxaemia, will therefore be discussed in some detail. Under resting conditions, ascents to high altitudes are not associated with true dyspnoea, no matter how severe the anoxaemia (Barcroft, Binger, Bock, Doggart, Forbes, Harrop, Meakins and Redfield, 1922; Greene, 1933; Hurtado, Kaltreider, and McCann, 1934; Schubert, 1935; Haldane and Priestley, 1935; Anthony and Schaltenbrand, 1936; Monge, 1937; Fronius, 1933; Loewy and Wittkower, 1937). It is true that slight hyperventilation often occurs, usually ascribed to stimulation of the carotid sinus or gland, but this is seldom associated with increased respiratory effort. It bears no resemblance to the rapid and distressed respiration of pneumonia or heart failure. There is, therefore, no justification for naming anoxaemia as the immediate cause of dyspnoea at high altitudes.

It is true that dyspnoea on exertion is a characteristic of residence at high altitudes, but it is obvious from the preceding paragraph that anoxaemia cannot be the immediate cause. There remain two apparent possibilities, that it is due to the acid products of abnormal metabolism, or that it is

reflex in nature. In man there is no evidence that an acidosis ever occurs at high altitudes, and the administration of ammonium chloride certainly does not increase dyspnoea on exertion (Haldane and Priestley, 1935; Barron, Dill, Edwards, and Hurtado, 1937). On the other hand, there is ample evidence that the dyspnoea on exertion which occurs at high altitudes is in the same category as cardiac dyspnoea. The myocardium is particularly susceptible to lack of oxygen (van Liere, 1936; Buchner, 1937), and animals exposed to anoxaemia for any length of time show all the concomitants of heart failure (Schneider, 1932; Campbell, 1935; Hurtado, 1932). The vital capacity is diminished (Verzár, 1933; Schneider, 1932; Hurtado, Kaltreider, and McCann, 1934) and *post mortem* the lungs are found to be congested. It is reasonable to suppose that the dyspnoea on exertion which occurs at high altitudes is essentially the same as cardiac dyspnoea. It is primarily reflex in origin. Chemical stimulation of the respiratory centres due to acid products of metabolism and stimulation of the carotid sinus by anoxaemia may have some secondary importance.

The clinical lesson to be learnt from the respiratory response to residence at high altitudes is not that anoxaemia causes dyspnoea, but that anoxaemia is particularly deleterious to the myocardium. Where the heart is already strained by pulmonary disease or myocardial damage, the relief of anoxaemia may be of the greatest therapeutic importance.

#### SUMMARY

In this review the causes of dyspnoea are discussed. It has been shown that though the conditions under which dyspnoea occurs are various and manifold, giving rise to an impression of complexity, the fundamental causes are few and relatively simple. They consist of chemical and reflex disturbances. The explanation of dyspnoea on chemical grounds has been popular in the past and appears at first sight reasonable and simple. As has been argued in this review, chemical dyspnoea would seem, however, to be of minor importance. Dyspnoea is usually reflex in origin and, in the forms of the greatest clinical importance, is associated with pulmonary congestion. For the rational treatment of impaired respiratory function an understanding of these fundamental mechanisms is essential.

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CARDIAC ANEURYSM<sup>1</sup>

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With Plates 27 to 31

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*Historical.*

THE term cardiac aneurysm was used by Lancisi (1740), de Senac (1783), Corvisart (1806) and their contemporaries to signify general enlargement of the heart cavities. In its present sense, cardiac aneurysm was first clearly defined by Baillie in 1793 as follows: 'It sometimes happens, although I believe very rarely, that the heart becomes aneurysmal. This disease consists in a part of it being dilated into a pouch, which is commonly more or less filled with coagulated blood.' From this time onwards the term partial aneurysm was often applied to the condition so defined by Baillie.

The first recorded case is attributed to Galeati (1757), though some doubt exists as to whether his case was a true aneurysm. In the same year Hunter described an undoubted example thus: 'At the apex it was forming itself into a kind of aneurism, becoming there very thin: that part was lined with a thrombus just the shape of the pouch in which it lay.' In 1785 Walter described a specimen of apical aneurysm which he had received long before, in 1759.

During the nineteenth century the condition became well recognized as a pathological rarity, and important papers on the subject were contributed by Breschet (1827), Thurnam (1836), and Legg (1883, 1884), who collected 90 cases observed subsequent to 1840. In this century Hall's paper (1903) dealing with 112 cases and Sternberg's exhaustive monograph (1914) are the most important studies.

Opinion on the pathology of cardiac aneurysm has undergone repeated changes. Breschet (1827) and Thurnam (1836) thought that rupture of the endocardium produced a false or dissecting aneurysm, and Thurnam (1836) also considered pericarditis as the cause rather than the consequence of aneurysm. Rokitsky (1842) distinguished two forms: acute aneurysm secondary to endocarditis, and chronic aneurysm secondary to fibrous degeneration of the heart wall. Cruveilhier (1827) also attributed aneurysm to myocardial fibrosis, a view that soon became generally accepted, though the cause of the fibrosis remained in dispute. Virchow (1859), Wilks (1857),

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and others attributed it to syphilitic or rheumatic inflammation. In 1881 Cohnheim, and also Ziegler, introduced the modern conception of ischaemic fibrosis due to coronary sclerosis or thrombosis; a view amply confirmed by Leyden (1884), Marie (1897), and many others. A full discussion of early pathological views is given by Sternberg (1914), who indicates that for almost a century cases had been reported under the three different titles of aneurysm, heart rupture, and angina pectoris, before it was realized that they were all manifestations of the same pathological process. He recognized four stages in the development of cardiac aneurysm: (1) Anginal attacks, (2) Infarction and pericarditis, (3) Latent period, (4) Terminal stage with congestive failure or sudden death.

Up to 1914 only three reported cases of cardiac aneurysm had been correctly diagnosed during life. Remlinger, in 1896, based the diagnosis on musical systolic and diastolic murmurs which were attributed to the passage of blood through the mouth of the aneurysmal sac, their gradual disappearance being explained by the sac becoming filled with clot. Voelcker's case was reported in 1902, the diagnosis being based on physical signs, but Sternberg's own case was the first to be diagnosed on what would to-day be considered the rational basis of its primary origin in coronary occlusion. Although no case of cardiac aneurysm had then been recognized by X-rays, Sternberg (1914) foresaw the possibility of radiological diagnosis, and mentioned calcification of the aneurysm as likely to be visible in the radiograph. In 1926 Pletnew was able to find in the literature only six cases correctly diagnosed during life.

Sézary and Alibert (1922) were the first to report a case of cardiac aneurysm diagnosed by means of radiological examination, although Kraus (1919) had reported an undiagnosed case of aneurysm found at necropsy, in which the X-ray findings during life were correlated with the post-mortem findings. Christian and Frik (1922) made the diagnosis of cardiac aneurysm by X-rays, but necropsy revealed an aneurysm at a site different from that of the bulge seen in the radiograph. Calcification of the wall of a cardiac aneurysm, reported by Thurnam and other early writers on the subject, was first recognized by X-rays during life by Determann (1932).

#### *Scope of Observations.*

Such miscellaneous conditions as extreme dilatation of the left auricle, congenital bulges of the cardiac septa, mycotic pouches on the valves, and aneurysms of the coronary vessels, may, strictly speaking, be included under the term cardiac aneurysm, but, as they have little in common, either clinically or pathologically, with the type of ventricular aneurysm with which we are concerned here, we shall not consider them further. The present paper deals with ventricular aneurysms, usually resulting from coronary occlusion and involving the left ventricle. It is based on a clinical and radiological investigation of 15 cases, five with necropsies.

*Group I (Cases 1-5).* Five cases in which cardiac aneurysm was found

at necropsy. All had been examined clinically and radiologically during life, and in three of them the clinical diagnosis of cardiac aneurysm had been made.

*Group II* (Cases 6-15). Ten patients in whom a diagnosis of cardiac aneurysm was made on clinical and radiological grounds, but in whom necropsy confirmation is not available, either because the patient is still alive or because permission for necropsy was not obtained.

In addition, the pathology is briefly discussed and data are given from a small series of 16 necropsies composed of the five cases in Group I and 11 other cases of which we have records.

#### *Pathology.*

The rarity of cardiac aneurysm has been much emphasized in the past. Thus Legg (1884) saw three aneurysms of the left ventricle in 1,890 necropsies during nine years at St. Bartholomew's Hospital; and according to Sternberg (1914), Huchard saw only three examples during 15 years, and Emmerich 15 in 8,660 necropsies at Munich. Prior to Sternberg's monograph, the pathology of cardiac aneurysm and its relation to coronary occlusion was not generally understood, and the term was probably used in a more restricted sense than to-day, so that these older statistics scarcely give a true conception of its frequency. In more recent post-mortem statistics relative to coronary occlusion and cardiac infarction or gross fibrosis, Levine (1929) recorded three cardiac aneurysms in 46 necropsies, Gibson (1925) eight in 50 necropsies, Lisa and Ring (1932) five in 100 necropsies, Parkinson and Bedford (1928) five in 83 necropsies, Cabot (1926) seven in 91 necropsies, and Wright-Smith (1936) 13 in 87 necropsies. Combining these figures we find that cardiac aneurysm occurred in 9 per cent. of cases of cardiac infarction examined at necropsy. If this is so, then cardiac aneurysm must be encountered not infrequently by those seeing many cases of coronary thrombosis in practice.

*Aetiology.* We have assembled the necropsy records of 16 cases of cardiac aneurysm accumulated during and since a previous investigation of coronary thrombosis, and including the five necropsy cases of the present paper.

The aetiological varieties of ventricular aneurysm are as follows:

- (1) Arteriosclerotic; sequel of coronary occlusion and cardiac infarction.
- (2) Syphilitic; due to focal gummatous myocarditis.
- (3) Mycotic; secondary to infective endocarditis.
- (4) Rheumatic; due to rheumatic necrosis of the myocardium.
- (5) Congenital; either aneurysms of the pars membranacea septi or cardiac diverticula.
- (6) Traumatic.

By far the commonest cause of aneurysms of the left ventricle is coronary occlusion. Virchow (1859) and others attributed cardiac aneurysm to syphilis and such cases were often reported in early papers, but the evidence of a syphilitic origin was often unconvincing, and many of them were

doubtless due to cardiac infarction. On the other hand a few well-substantiated cases are on record (Cookson, 1929; Morris, 1927; Benson, Hunter, and Manlove, 1933; Sohval, 1935; Brenner, and Wachner, 1936). Even when syphilitic aortitis is present, cardiac aneurysm may be due to myocardial infarction. Sternberg (1914) states that of 207 published cases of cardiac aneurysm in which the aetiology was reasonably certain, 174 or 84.8 per cent. were due to coronary occlusion.

In this pathological series of 16 cases, 13 were due to coronary occlusion; in 11 the left anterior descending branch was occluded, two with occlusion of the right coronary in addition, in one the right coronary only, and in one the left circumflex coronary. Of the remaining three cases, all had rheumatic valvular disease; in one (Case 3) there was an apical aneurysm which Professor H. M. Turnbull attributes to scarring of rheumatic necrosis of the myocardium, in another there was an aneurysm of the pars membranacea septi, and in one a small basal aneurysm just below a bicuspid aortic valve affected by rheumatic endocarditis.

*The form of the aneurysm.* In some cases the aneurysm is saccular, communicating with the ventricular cavity by a definite neck or orifice. More often, an old infarct yields to form a pouch or bulge which is not sharply demarcated from the main ventricular cavity. Sternberg (1914) holds that external bulging is not essential, and that pouches or small cavities in the cardiac wall, which often contain clots, should be regarded as aneurysms. The size of the aneurysm varies from that of a small nut to that of the large aortic aneurysms, and Legg (1884) mentions a case where the sac was larger than the heart itself. Shennan and Niven (1925) describe a case in which the greatest diameter of the sac was 16 cm., which they claim to be the largest on record.

*Site.* Aneurysm due to occlusion of the anterior descending coronary artery is usually situated at the apex, but quite commonly it involves the anterior wall of the left ventricle above the apex. Aneurysm of the posterior wall of the left ventricle is relatively rare, though infarction of this wall is quite frequent. Aneurysms due to other causes may involve any part of the left ventricle, especially the base or septum. In our 16 necropsies the aneurysm was at the apex in eight, on the anterior wall of the left ventricle in three, and in both these places in one case; in only two cases was the aneurysm on the posterior wall, in one of which it also involved the apex. In the remaining two cases, not due to coronary occlusion, the aneurysm was just below the aortic orifice in one case, and involved the septum in the other. In Thurnam's (1836) 66 cases where the site is specified, the aneurysm was at the apex in 27, and involved other parts of the wall in 39, 21 of which were at the base. In Legg's (1884) 90 cases, there were 50 apical aneurysms and 31 elsewhere, and in Loebel's (1840) 72 cases there were 39 at the apex, 22 at the base, and 16 elsewhere in the left ventricle. The extreme rarity of aneurysm of the right ventricle is shown by the fact that Legg found only three reported cases.

*Structure.* The wall of the aneurysm is usually thin and composed entirely of fibrous tissue, but occasionally a little muscle is left. The pericardium over the sac is almost always adherent. The interior of the sac usually contains clot, and often it is laminated and organized as in an aortic aneurysm. Calcification of the clot has been reported (Jaksch-Wartenhorst, 1928). Calcification of the wall of the aneurysm was present in three of our necropsy cases, in one of which the endocardial surface only was affected. Hochrein (1937) portrays a calcified aneurysm in which the pericardium was calcified, though he also says that calcium was present in the myocardial scar. The point is important in X-ray diagnosis, as a calcified aneurysm has to be differentiated from constrictive pericarditis with calcification. Calcification of the sac was recorded in the early cases of Corvisart (1806) and Cruveilhier (1827), and was noted by Thurnam (1836) in six cases and by Legg (1884) in 10 cases.

Rupture of the aneurysm was not found in any of our specimens, confirming the general experience that rupture of the heart is usually due to recent infarction, and is uncommon in aneurysm. It occurred in six of Thurnam's (1836) 58 cases, in 17 of Hall's (1903) 112 cases. Benson, Hunter, and Manlove (1933), in 40 cases of ruptured heart, found an aneurysm in seven cases, and in three of these rupture was due to superadded recent infarction. In Goodall and Weir's (1927) 18 cases of ruptured heart, there was no case of aneurysm.

#### *Clinical Features*

*Incidence.* The only reliable criteria regarding the incidence are to be obtained from necropsy statistics, and these have already been discussed. Of the 15 cases in this series, 14 were males and only one case was female. These figures may be compared with those based on necropsies collected by Thurnam (1836), who found that 30 were males and 10 females; Legg (1884), 64 males, 24 females; Hall (1903), 59 males, 21 females; and Sternberg (1914), 65 per cent. males. The age limits of our cases were 30 to 74, the average age being 56. In Thurnam's series (1836), the limits were 18 to 81. Legg (1884) found 12 cases in the age group 20-29, and nine in the age group 70-79, with a maximum incidence of 19 from 50-59 years. Hall (1903) reported one case under the age of 20, four cases over 80, and 41 between the ages of 40 and 70.

*Symptoms and signs.* A study of the literature on the subject shows that, before the advent of radiology, no satisfactory signs diagnostic of cardiac aneurysm were known. Aubertin and Lereboullet (1929), from an analysis of published cases, give the following list of clinical signs: increased area of cardiac dullness; increase of praecordial pulsation, often not coinciding with the apex-beat; bruit de galop; a systolic or a double murmur at the apex; pericardial friction. Strandell (1930) gives a similar list.

In 11 of our cases, a diagnosis of coronary thrombosis was made either

from direct observation of the acute attack, or from a history of such an attack. Of the remaining four cases, two gave a clear history of angina of effort, one of them over a period of nine years, and culminating in attacks of nocturnal dyspnoea, while two did not admit that they had experienced anginal pain, their symptom being dyspnoea on exertion, which proved the forerunner of congestive heart failure. Pain over the apex, a feature stressed by Lutembacher (1920), and mentioned by Kahn (1922), was not noted in our patients, but one of them (Case 14) complained of tenderness in this region. In the 11 cases with a history of coronary thrombosis, the average interval between the attack and the diagnosis of cardiac aneurysm was  $17\frac{1}{2}$  months, the extremes being three months and seven years. Cardiac aneurysm appearing within a week or two after coronary occlusion has been reported (Shookhoff and Douglas, 1931), and in several cases after an interval of only a few months (Pinchin, 1930; Fogel, 1933; Friedlander and Isaacs, 1920; Jervell, 1935).

In the majority of our patients, the apical impulse was displaced outwards, diffused over a wider area than normal, and often unduly forcible or heaving. In one patient (Case 5) there was a localized, expansile, systolic pulsation in the third left interspace four inches from the midline, separate from, and above the apex-beat. Strauch (1900), and Libman and Sacks (1926) stress this feature, the presence of a pulsation over the aneurysm, separate and distinct from the apical pulsation. Scherf and Erlsbacher (1934) describe as a typical pulsation in cardiac aneurysm one separate from the apex-beat, situated above and mesial to it, which appears a week or two after coronary thrombosis, and tends to disappear after a few weeks. In only two of our patients was there no displacement of the apex-beat, and in one no apex-beat was palpable. Heaving pulsation of the whole praecordium was twice observed. The heart sounds were often noted as faint or muffled, but occasionally they were of normal intensity. A short, apical, systolic murmur was common. It is of historical interest to note that Remlinger (1896) gave a double murmur as one of the signs of cardiac aneurysm, a sign which Strauch (1900) and Scherf and Erlsbacher (1934) also mention, but it was not detected in any of our patients.

In no case was the blood-pressure found raised while under our observation, though in contrast the heart was often large. The pressure usually varied between 100 and 130 mm. Hg systolic, levels below 120 mm. being recorded in seven patients; but only as a transient or terminal event did it fall below 100 mm. These figures are comparable with those reported by other workers, an analysis of 45 cases collected from the literature giving an average of 130/75 mm. That hypertension in the past does not exclude the subsequent formation of a cardiac aneurysm is shown by certain published cases, such as those of Mackenzie (1923), 210 mm. systolic; Brunet (1926), 190/110 mm.; Levine (1929), 210/135; Boller and Pape (1932), 235/130. Although there is a history or evidence of past hypertension in about 70 per cent. of all cases of cardiac infarction (Palmer, 1937), we did

not find any such evidence in our series of cases of cardiac aneurysm. This fact raises the possibility that the thickened wall of a heart hypertrophied from hypertension is less prone to yield when infarcted than a heart not so thickened.

Paroxysmal tachycardia occurred in three cases, in two of which it was recorded and proved to be of the ventricular type. In all the others, normal rhythm was present. Paroxysmal ventricular tachycardia has been reported twice (Parade, 1934; Scherf and Erlsbacher, 1934), auricular flutter once (Jervell, 1935), and auricular fibrillation six times, in three of which it was confirmed by electrocardiogram (Cookson, 1929; Strandell, 1930; Parade, 1934).

In 13 of our cases electrocardiographic tracings characteristic of infarction of the anterior wall of the left ventricle were obtained, showing inversion of  $T$  in Lead I or Leads I and II, or  $R-T$  elevation in Lead I, and often a prominent  $Q_1$ . In only one case was there a  $T_3$  type of curve indicating posterior wall infarction. In the remaining case the only electrocardiogram showed paroxysmal ventricular tachycardia. Of 21 cases reported in the literature, there were 17 with a  $T_1$  type of curve and only four with a  $T_3$  curve.

Sometimes a degree of congestive failure was present when the patient was first seen, and this persisted; but in others the disability seemed remarkably slight. One patient (Case 2) was subject to severe anginal attacks over a period of  $8\frac{1}{2}$  years, and finally to attacks of nocturnal dyspnoea.

#### *Clinical Course and Prognosis*

In those patients who have died, the period elapsing between the attacks of coronary thrombosis and death varied between nine months and five years, averaging twenty-three months. Between the first diagnosis of cardiac aneurysm and death the period ranged from one week to thirty months, averaging ten months. Of the seven patients dead, four died from congestive heart failure, two died suddenly, and one succumbed to a cerebral embolism. This is a not infrequent complication of cardiac infarction, and as a late complication, i.e. several months or years later, it is suggestive of cardiac aneurysm; it occurred in three of our 15 patients.

Some patients are surprisingly well, considering their disease. None of ours can vie with Wilson's (1919) patient who walked one mile to church less than twenty-four hours before her death from a ruptured cardiac aneurysm, and, although aged 60, could never remember being ill and thought nothing of walking twenty miles. But several of our patients were able to live a comparatively active life.

#### *Radiology*

The first contribution of importance to the radiology of cardiac aneurysm was made by Lutembacher (1920), who described two cases recognized at necropsy, in which X-ray examination during life had failed to reveal the aneurysm, showing only enlargement of the heart to the left. He pointed

out that aneurysms were usually apical, and that they were often buried in the diaphragm and invisible in the radiograph. Sézary and Alibert (1922) were the first to recognize cardiac aneurysm by X-rays, which, in their case, showed a localized bulge on the contour of the left ventricle, just above the apex; radioscopy by Bordet revealed slight expansion of this aneurysm during systole. Christian and Frik (1922) diagnosed cardiac aneurysm by reason of a hump in the middle of the left ventricular border in the radiograph, but at necropsy this hump proved to be the hypertrophied wall of the left ventricle above an aneurysm located on the anterior wall near the apex. Heitz and Corone (1923) described typical radiographs of an aneurysm of the left ventricle above the apex, and in discussing the diagnosis they postulated systolic expansion of the aneurysmal shadow as essential. Some of the early published radiographs purporting to show cardiac aneurysm would to-day suggest aneurysm of a sinus of Valsalva, but quite a number of observations have now been recorded in which the diagnosis seems beyond doubt or was verified by necropsy. The more important of these are found in the papers of Kalisch (1927), Strandell (1930), Harvier and Caroli (1930), Pinchin (1930), Alvarez (1931), Calandre and de la Puerta (1931), Shookhoff and Douglas (1931), Ellman (1932, 1934), Boller and Pape (1932), Determann (1932), Fogel (1933), Groedel (1933), East (1933), Parade (1934), and Steel (1934).

In general, the diagnosis of aneurysm depends on the following radiological findings:—

- (1) Enlargement of the left ventricle with deformity of its contour.
- (2) A localized protuberance inseparable from the heart shadow on rotation of the patient.
- (3) Abnormal or absent pulsation of the aneurysmal zone.
- (4) Evidence of adhesions between the heart and the chest wall or diaphragm.
- (5) Calcification of the wall of the sac or of its contained clot.

The deformity of the ventricular contour is usually visible in the anterior and often in oblique radiographs, and will be discussed in relation to the site of the aneurysm. Routine oblique radiographs may fail to demonstrate an aneurysmal bulge adequately, so it is necessary first to determine the optimum obliquity by screen examination. The tendency for apical aneurysms to be buried in the diaphragm explains the absence of radiological evidence in some cases, as first indicated by Lutembacher (1920), and as exemplified by Ellman's (1932, 1934) case, where an anterior aneurysm was recognized, but an additional apical one was concealed by the diaphragm. This difficulty may be overcome to some extent by inflating the stomach with gas by means of an effervescent drink, a procedure we have found of great help in visualizing the apex. Screen examination is most important, and cannot safely be omitted; for the eye can fix the heart in systole when an aneurysmal bulge is most obvious, and watch the cardiac pulsation and diaphragmatic movements.

Much importance has been given in the past to systolic expansion of the aneurysmal bulge, but it is now rightly admitted that appreciable expansile pulsation may be absent. When the wall of the sac is reinforced by laminated clot within and by thickened adherent pericardium without, or when it is calcified, little pulsation is to be expected, especially as the systolic pressure is usually low. In our Case 5, expansile systolic pulsation of the sac was obvious on the screen, and could easily be felt with the hand on the chest wall, but as a rule we found it difficult to be certain about systolic expansion, for pulsation in the region of the aneurysm was usually diminished or absent, or at least abnormal.

Kymography has been applied to the study of the localized cardiac infarct, apart from cardiac aneurysm. Schilling (1933) was the first to demonstrate absence of normal pulsation over an infarct at the lower half of the left ventricular wall confirmed at necropsy. The subject is elaborated by Stumpf, Weber, and Weltz (1936), who describe diminished range of movement and a systolic lateral movement as indicating the site of a cardiac infarct. In cardiac aneurysm, confirmed by necropsy, a paradoxical pulsation—expansion of the sac during ventricular systole—has been recorded by kymograph (Braunbehrens, 1934), and striking absence of movement over a circumscribed area near the apex in a case diagnosed as aneurysm (Heier, 1936). It is worth remembering that in great cardiac enlargement, from other and more usual causes, there may be remarkably little visible pulsation near the apex. Diagnosis of cardiac aneurysm from this sign alone should therefore not be made too readily.

The rate of development of enlargement in cardiac aneurysm can be judged to some extent by the period elapsing between the date of the coronary thrombosis and the appearance of a demonstrable aneurysm as seen on the radiograph. Of five cases where serial radiographic observations were made, two showed no increase in size over one year, two increased about  $\frac{1}{2}$  cm. at the site of 'ledging' in one year and two years respectively, and the remaining case increased  $\frac{1}{2}$  to 1 cm. over the whole of the aneurysmal convexity in four years.

In the literature a small cardiac aneurysm has been shown to develop within two months of the attack of coronary thrombosis (Jervell, 1935; Hochrein, 1937). Serial records are of interest not only in respect of the degree and rate of enlargement (Ellman, 1932, 1934; Steel, 1934), but also of the changing shape of the ventricular silhouette (Clerc, 1937; Semerau-Siemianowski, 1937; Poix and Thoyer, 1937).

In the past aneurysms have been described as involving the apex, base, or anterior wall of the heart; but now they should be grouped with their parent infarct as anterior or posterior according to the coronary branch occluded, thereby also corresponding to the two main electrocardiographic patterns. Anterior aneurysms usually involve the apex to some extent, but posterior aneurysms need not do so.

*Aneurysm of the Anterior Wall of the Left Ventricle.*

*Anterior position.* The heart is usually though not always enlarged to the left, and its contour is deformed. The aneurysm often involves the lower half of the left ventricular contour, in which case the apex appears broadened or blunted, giving the heart a square or rectangular appearance. There may be an angular deformity of the left heart border, and the angle may project to the left beyond the apex proper, as in Case 6 (Plate 27, Fig. 4), and in cases described by Pinchin (1930) and by Fogel (1933). If the aneurysm grows mainly towards the left, the heart appears elongated towards the left chest wall, with its apex blunted (Plate 29, Fig. 11). The aneurysm may project from the upper half of the left ventricular contour, either as a diffuse bulge, or more rarely as a localized hump. An anterior aneurysm growing directly forwards may be invisible from the front, though rotation into the right oblique position discloses it, as in Case 5 (Plate 27, Figs. 2, 3), and in one of East's (1933) cases. It is not always easy to determine whether a bulge of the left heart border is formed by the aneurysm itself or by the left ventricle displaced upwards by an apical aneurysm as in the classical case of Christian and Frik (1922). Fixity of the apex, restricted movement of the left diaphragm, and adhesions between pericardium and diaphragm can sometimes be detected.

*Right oblique position.* This is especially favourable for visualizing an aneurysm projecting forwards from the anterior ventricular wall. Typically, the aneurysm projects forwards so that its upper margin forms a more or less abrupt ledge or shelf on the anterior contour of the heart, and we have come to regard this 'ledging' in the right oblique position as one of the most important signs of cardiac aneurysm. It is well seen in Plates 29-31, Figs. 10, 13 and 15, and in Case 5 (Plate 27, Fig. 3) in which the aneurysm was invisible in the anterior view. It is sometimes impossible to separate the heart shadow from the chest wall in full inspiration, and the heart may move upward with the chest instead of downward with the diaphragm in inspiration as it may in adherent pericardium. Undue prominence of the left auricle posteriorly was noticed in two of our cases, presumably due to a backward displacement of the heart by an aneurysm situated anteriorly.

*Aneurysm of the posterior wall of the left ventricle.* This rare type of cardiac aneurysm was seen once (Case 7) and was localized both by electrocardiogram and by X-rays. The anterior radiograph shows a diffuse bulge at the upper part of the left ventricular border, separated by a notch from the left ventricle proper (Plate 28, Fig. 5). In comparison with an anterior wall aneurysm it is situated at a higher level, otherwise its appearance is similar. In this case the left oblique radiograph is diagnostic; for it shows the aneurysm projecting backwards from the upper part of the posterior wall of the left ventricle, and indenting the barium-filled oesophagus (Plate 28, Fig. 6). Because it has expanded upwards, it is visible from the front, above the left ventricle proper. Aneurysms of posterior type tend to involve the base or middle zone of the ventricle rather than the apex, and,

if small, will be invisible from the front, as was reported by Roubier and Gonnet (1936) and by Strandell (1930). Brenner and Wachner (1936) described a case showing, in the anterior radiograph, a semicircular calcified projection in the region of the left hilum above the heart; this was thought to be a cyst or even an aortic or pulmonary aneurysm, but necropsy showed it to be an aneurysm of the upper part of the posterior wall of the left ventricle. These aneurysms, being adjacent to the oesophagus, may displace it and even cause dysphagia (Strandell, 1930; Wolferth and Wood, 1935). Whenever a posterior aneurysm is suspected because of a  $T_3$  type of electrocardiogram, examination in the left oblique position with a barium swallow should be carried out with a view to locating the aneurysm posteriorly.

*Aneurysm of the interventricular septum.* Besides aneurysms of the pars membranacea, which are usually of congenital origin, infarcts involving the septum occasionally yield to form an aneurysm which bulges into the right ventricle. The X-ray picture of such a case, verified at necropsy, has been described by Boller and Pape (1932). They found extreme enlargement of the heart to the right although there was no clinical explanation for right-sided enlargement. We have observed a similar X-ray picture in a patient with typical clinical and electrocardiographic evidence of coronary thrombosis, the only explanation of which appeared to be a septal aneurysm.

*Calcification of the wall of a cardiac aneurysm* was demonstrated radiographically in a post-mortem specimen by Simmonds (1908). Jaksch-Wartenhorst (1928) described a case in which a calcified intracardiac shadow near the apex, seen in the radiograph, proved to be calcified clot within a cardiac aneurysm. Determann (1932) reported a case in which radiographs showed a linear calcification just within the left heart border, thought to be due to calcified pericardium, but necropsy revealed a cardiac aneurysm with calcification in the wall. A radiograph of a calcified cardiac aneurysm is given by Hochrein (1937), and necropsy showed calcification and obliteration of the pericardium, though it is also stated that calcium was present in the myocardial scar. Calcification was seen in the radiographs of three of our cases. In Case 2 the anterior radiograph showed a semicircular line of calcium within the left ventricular border, and curving inwards from the external surface at its upper and lower ends (Plate 27, Fig. 1). Necropsy showed the calcium to be situated on the endocardial surface of the aneurysmal wall. In Cases 9 and 10 linear calcification was visible outlining the aneurysmal bulge in the anterior view, and in the former case an annular calcified shadow was visible in both oblique views, outlining the ledge in the right oblique (Plate 28, Fig. 8).

Calcification of a cardiac aneurysm has to be differentiated from calcified pericardium such as may occur in constrictive pericarditis, and this has been discussed by Determann (1932). In aneurysm the calcified shadow is linear and even, is situated within the heart contour, and is limited to the left ventricle, while calcification of the pericardium produces a thicker and more irregular shadow, outside the heart shadow, and not restricted to the left

ventricle. Mentl (1931) describes a case of calcified pericardium, verified at operation, in which a hernial protrusion of the left ventricle through an aperture in the calcified coat, seen on radioscopy, at first suggested a ventricular aneurysm. A similar hernial protrusion was described by Vilvandr  (1930) in a calcified pericardium. Comparison of radiographs of these two conditions suggests that they can be differentiated on purely radiological grounds, but in actual practice the history and clinical signs would also be distinctive. Calcification of a valve can be identified without difficulty, and the shape and position of the shadows will exclude calcified aneurysm.

*Negative X-ray findings.* In two of our cases (3 and 4) in which aneurysms were found at necropsy, radiographs had shown only cardiac enlargement. Both patients were extremely ill and died shortly after admission, so that only routine radiographs were obtained. More complete radiological investigation might have revealed evidence of aneurysm, and this applies to many of the negative X-ray findings recorded. It is obvious that very small aneurysms must escape detection, but we believe that aneurysms of appreciable size can almost always be visualized by X-rays, provided that careful search is made. Routine films are not sufficient, for screen examination is necessary to find the optimum position for displaying the aneurysm, and in addition for observing the mobility and pulsation of the heart. Inflation of the stomach with gas will minimize the chance of overlooking an apical aneurysm.

#### *Differential Diagnosis.*

When cardiac aneurysm is in question, due weight will naturally be given to the history, symptoms, signs, and electrocardiogram, in so far as they indicate coronary thrombosis, but a positive diagnosis will generally depend on radiological investigation. It is necessary, therefore, to have in mind and to exclude other pathological conditions the radiological picture of which may simulate that of cardiac aneurysm.

In a patient with normal or low blood-pressure, known to have had coronary thrombosis, a rounded and enlarged left ventricle with little pulsation must now raise the possibility of a cardiac aneurysm being present. In fact, the only other likely explanation would be a previous hypertension which had not been recognized. Though cardiac aneurysm may be suspected in such a case, it can be diagnosed with certainty only if there is ledging or deformity of the left ventricular contour, or if characteristic calcification is discovered. We have been impressed by the discrepancy between the large size of the left ventricle and the slender vascular pedicle in the radiographs of cardiac aneurysm (e.g. Plates 27, 28, Figs. 1, 5, 7). In hypertension the large left ventricle is commonly associated with a broad vascular pedicle from unfolding of the aorta, and often this has some relation to the size of the left ventricle.

An enlarged conus arteriosus of the right ventricle projecting at the upper half of the left heart border may occasionally simulate aneurysm, but signs

of mitral stenosis or perhaps of congenital heart disease will almost certainly be present. The same applies to a greatly dilated pulmonary artery which lies still nearer the aortic knuckle, level with the hilar vessels. Rarely the left auricle in mitral stenosis projects to the left beyond the conus, giving a bilocular appearance to the left heart border.

Aneurysms of the descending aorta may project to the left, beyond and, of course, behind the left ventricle, when viewed from the front, but rotation of the patient will separate the aneurysmal shadow from the heart. Aneurysms of a sinus of Valsalva may extend upwards and to the left, projecting from the upper part of the left ventricular border in the region of the conus of the right ventricle (Plate 31, Fig. 18). Being more or less embedded in the heart, these aneurysms may closely simulate the X-ray picture of cardiac aneurysm, and a diagnostic error in either direction may occur (Brenner and Wachner, 1936; Schuster, 1937). A positive Wassermann reaction and signs of aortic incompetence will favour the diagnosis of a sinus aneurysm in such a case.

The radiological diagnosis between calcified pericardium and cardiac aneurysm has already been discussed; the clinical diagnosis may depend on the presence of signs of constrictive pericarditis (Pick's Disease). Pericardial effusion is occasionally loculated and limited to one side of the heart (Wessler and Fried, 1928), or an organized exudate may form a cyst (Yater, 1930) or diverticulum of the pericardium, though the latter usually presents on the right side (Cushing, 1937).

Between the cardiac apex and the left dome of the diaphragm is often seen a small triangular shadow (para-apical triangle) of less density than the heart and frequently containing fat. It might needlessly suggest cardiac aneurysm in a patient who had had coronary thrombosis.

Non-cardiovascular tumours in the chest such as dermoid or hydatid cysts, neoplasms, or even loculated effusions may happen to lie adjacent to the heart, and to simulate cardiac aneurysm in the radiograph, but the absence of a coronary history and of typical electrocardiographic changes will almost exclude it.

### *Summary*

(1) The evolution of our knowledge of cardiac aneurysm and its morbid anatomy is shortly reviewed.

(2) Cardiac aneurysms are usually due to coronary occlusion with resultant infarction, and rarely to syphilis, infective endocarditis, congenital defects, or trauma. A detailed necropsy report is given of a case ascribed to rheumatic necrosis of the myocardium.

(3) Cardiac aneurysms, like infarcts, involve the left ventricle almost exclusively, and may best be classified as anterior or posterior, according to the coronary branch occluded. The great majority involve the anterior wall of the left ventricle, usually at or near the apex.

(4) The clinical and radiological features of 15 cases of cardiac aneurysm are described, and in five of them the diagnosis was confirmed by necropsy. The significant clinical features are a history of coronary thrombosis, enlargement of the heart to the left, a normal or low blood-pressure, distant heart sounds, and an electrocardiogram most often indicative of anterior infarction ( $T_1$  type). Expansile pulsation separate from the apex-beat, or an extensive area of praecordial pulsation, are rare but suggestive signs.

(5) Diagnosis depends mainly upon radiological examination. Anterior aneurysms cause enlargement of the heart to the left, with deformity of its contour. This deformity, seen from the front, may take the form of (i) broadening of the apex or angulation of the left border, giving the heart a square or rectangular appearance; (ii) elongation of the heart to the left; (iii) a diffuse bulge or, more rarely, a localized hump on the left border. In the right oblique position, 'ledging' of the anterior heart border is of great diagnostic value. Posterior aneurysms are best seen in the left oblique position, and may displace the oesophagus. Aneurysm of the interventricular septum has been known to cause enlargement of the heart to the right. Calcification of the aneurysmal wall, when present, is an invaluable sign. Radioscopy is essential to determine the optimum position for demonstrating the aneurysm, to observe the character of the pulsation, and to detect localized adhesion.

(6) The differential diagnosis has to be made from an enlarged right ventricular conus, aortic aneurysm, especially that involving a sinus of Valsalva, calcified pericardium, loculated pericardial exudate or cyst, the para-apical triangle of fat, and from intrathoracic neoplasm or cyst.

We are indebted to Drs. Donald Hunter, William Evans, and John Hunt for permission to record Cases 6, 3, and 13 respectively. We thank Professor H. M. Turnbull and Dr. W. W. Woods for necropsy reports, especially that on Case 3, and also Professor James McIntosh.

#### *Case Reports*

##### *Case 1. Male, aged 50.*

*History.* Syphilis aged 20. In February, 1933, severe attack of substernal pain, radiating to left arm, lasting four hours. Subsequent liability to pain and tenderness below left nipple, provoked by effort and relieved by rest.

*Examination* (June, 1933). Pulse 90, regular. Arteries thickened and tortuous. Blood-pressure 140/90 mm. Hg. Apex-beat heaving, 6th and 7th interspaces in anterior axillary line. Heart sounds distant. Broadbent's sign present. Wassermann reaction negative.

*Electrocardiogram.* Normal rhythm, QRS widened and notched in all leads, elevation of  $R-T_1$  and  $R-T_2$ .

*X-ray.* Anterior; gross enlargement of heart, mainly of left ventricle, with blunting of apex (Plate 31, Fig. 14). Right oblique; ledging of anterior heart border, and abnormal prominence of left auricle posteriorly.

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* August, 1933, in hospital on account of dyspnoea and pulmonary oedema. November, 1933, readmitted on account of increasing dyspnoea, cough, and haemoptysis. Signs of congestive heart failure present, blood-pressure 120/80 mm. Died in December, 1933.

*Necropsy* (L.H. P.M. 530/1933). Heart weight, 1474 gm. Aneurysm of apex of left ventricle (internal diameter 10 cm.; projecting on outer surface at least 2.5 cm. above the plane of right ventricle). Moderately dense fibrous adhesions between visceral and parietal pericardium over aneurysm. Wall of aneurysm (0.15–0.3 cm. thick) composed of dense fibrous tissue, lined internally with adherent laminated clot (up to 4 cm. thick). Slight hypertrophy and dilatation of upper non-infarcted part of left ventricle (1.6 cm. thick) and of right ventricle (0.5 cm. thick). Anterior descending coronary artery greatly stenosed by atheroma and an old organized thrombus 2.5 cm. from its origin. Atheroma without stenosis of other coronary branches. Two recent infarcts of right lung. Old infarct of spleen.

*Necropsy diagnosis.* Heart failure. Aneurysm of heart. Old fibrosis of myocardium. Old thrombus in coronary artery stenosed by atheroma.

*Case 2.* Male, aged 60.

*History.* In July, 1926, attended hospital with angina of effort of two years' duration. Heart enlarged to left; blood-pressure 130/80 mm.; electrocardiogram, inversion of  $T_1$  and  $T_2$ . First seen by us in March, 1932, with anginal pain on effort and nocturnal dyspnoea. No history of coronary thrombosis obtained.

*Examination.* Pulse regular. Arteries normal. Blood-pressure 120/80 mm. Apex-beat displaced into anterior axilla. Heart sounds at apex muffled and distant. Liver slightly enlarged, no oedema. W.R. negative.

*Electrocardiogram.* Normal rhythm, left axis deviation, QRS widened in all leads, inversion of  $T_1$ .

*X-ray.* Anterior; considerable enlargement of heart to left, with blunting of apex. A linear shadow of calcification just within the left ventricular border and extending along its whole length (Plate 27, Fig. 1). Right oblique; ledging of the anterior heart contour, and abnormal prominence of the left auricle posteriorly. Radioscopy; absence of pulsation at the apex, visible adhesions between pericardium and left diaphragm, and upward movement of heart in inspiration.

*Diagnosis.* Coronary occlusion. Calcified aneurysm of anterior wall of left ventricle.

*Course.* Anginal pain diminished, and nocturnal dyspnoea became more frequent. Blood-pressure fell to 105/80 mm. October, 1932, died suddenly.

*Necropsy* (heart only). Heart weight, 624 gm. Left ventricle much enlarged and posterior wall hypertrophied. An old fibrous infarct involved a large part of anterior wall of left ventricle and septum, with two aneurysmal bulges. One, from the upper part of anterior wall, 6.5 × 7.5 cm. in size, was filled with old laminated clot, and its endocardial surface was calcified. The other pouch was at the apex, and was also calcified on its endocardial aspect. Pericardium over left ventricle adherent. Severe coronary atheroma with occlusion of left anterior descending branch, and stenosis of right coronary artery.

*Necropsy diagnosis.* Coronary occlusion. Two aneurysms of left ventricle, both calcified.

*Case 3.* Female, aged 42.

*History.* Two weeks before admission, sudden onset of palpitation in bed,

recovery by next morning. A week later, while dancing, recurrence of palpitation which persisted till admission. No history of rheumatic fever.

*Examination.* Pulse 225, regular. Blood-pressure 100/60 mm. Apex-beat diffuse, 5th interspace in mid-axillary line. Heart sounds distant, no murmurs. Liver enlarged.

*Electrocardiogram.* Ventricular tachycardia, rate 225.

*X-ray.* Anterior view, enlargement of heart, increased hilar shadows. Patient too ill for satisfactory examination.

*Diagnosis.* Paroxysmal ventricular tachycardia. Congestive heart failure.

*Course.* In spite of treatment, patient became weaker and died.

*Necropsy. Weights.* Body 40.1 kg. (length 1.5 m.); liver 1268.6 gm.; brain 1148.1 gm.; heart 318.9 gm.; kidneys 219.7 gm.; spleen 63.8 gm.; suprarenal bodies 18.9 gm.; thyroid 11.45 gm.; thymus (fatty) 7.1 gm.; ovaries 6.8 gm.; pituitary body 0.65 gm.

*Heart.* The wall of the apex of the left ventricle, in an area from 4.5 to 5 cm. in diameter, was about 0.4 cm. thick and bulged outwards to form an aneurysm. In microscopic sections the myocardium here is almost entirely replaced by dense fibrous tissue. The rest of the myocardium of the left ventricle contains areas, for the most part large, which show the following three types of change; the muscle fibres show recent hyaline necrosis or a partly fatty, partly coarsely granular and vesicular necrosis; the muscle fibres are partly or completely lysed, and fibroblastic proliferation is conspicuous; the myocardium is replaced by dense fibrous tissue. The fibroblastic proliferation is associated with an infiltration of varying amount; which includes mononuclear and multinuclear epithelioid cells such as are seen in rheumatic nodules; neutrophil leucocytes are very sparse. The myocardial muscle is hypertrophied, the greatest hypertrophy being in the small groups of fibres enclosed in the fibrotic apex. In sections from fourteen parts of the left ventricle and interventricular septum most of the intramyocardial arteries show no conspicuous change; the cytoplasm of the muscle cells in the media is pale and often vacuolated, while occasional nuclei are reduced to a small dot of chromatin. In some arteries, however, there is a definite local loss of medial muscle. More numerous are arteries in which the media is partly or completely replaced by dense fibrous tissue, while the lumen is surrounded by a stout musculo-elastic intima. The most obvious acute necrosis of arteries is seen in a papillary muscle attached to the mitral valve. The muscle of the apex of the papilla shows recent necrosis without cellular proliferation. In the centre of the apex there is a large recent haemorrhage. In the lower part of this is a large artery in which almost all the cells of the media have disappeared, while a zone of fibrin lies between the endothelium and internal elastic membrane. In the deeper part of the papilla the myocardial fibres show various stages of disintegration and lysis, associated with considerable fibroblastic proliferation and infiltration. Here the media of the arteries and arterioles contain few or no muscle cells, the internal and external elastic laminae in some enclosing a perfectly clear space. In cross-sections of the large coronary arteries in the subpericardium there are occasional crescentic areas of slight to moderate intimal hypertrophy with slight degeneration.

*Valves.* The cusps of the mitral valve were moderately thickened, the chordae tendinae were slightly shortened and thickened, and the mitral orifice was slightly stenosed (6.5 cm. in circumference). There was a ridge of tough, somewhat gelatinous, yellowish vegetation on the contact margins

of both cusps, and a similar ridge (0.6 cm. long) on the adjacent halves of the anterior and right cusps of the aortic valve. The aortic cusps appeared otherwise normal. The left auricle was slightly hypertrophied, but not dilated. In microscopic sections of the posterior cusp of the mitral valve there is great fibrotic thickening of the contact layers. A large superficial portion of this thickening has undergone fibrinoid necrosis. Within and near the fibrinoid mass are a few large epithelioid cells.

*Jejunum.* In a dilated loop (22 cm. long) in the centre of the jejunum there was great diffuse haemorrhage throughout all coats. The serous surface did not appear necrosed, and there was no fibrin upon it. The branches of the superior mesenteric veins were filled with thrombus, but the thrombus had the laminated structure of ante-mortem thrombus only in places and, then, in a narrow peripheral zone. The superior mesenteric artery and its branches contained no clot. The lumen of the gut contained red and brown blood as far as the centre of the ileum. Microscopically the jejunum, with the exception of the subserosa and outer layer of the muscularis, is necrosed. Haemorrhage is very great in the swollen submucosa and the necrosed inner layer of the muscularis, and is considerable in the subserosa. The largest arteries in the subserosa appear healthy. In most of the remaining arteries and arterioles some or all the muscle fibres of the media have been lysed, and the resulting spaces are filled with red corpuscles, while the elastic lamella is intact but flattened by dilatation of the vessel. Several other arterioles show fibrinoid necrosis. The capillaries contain hyaline thrombus. The veins are greatly engorged. Their media is extensively necrosed. Their lumina are lined with, and sometimes greatly narrowed by, a deep zone of neutrophil leucocytes covered by a shallow fibrinoid zone. This lining is sharply defined towards the lumen, and in some veins is covered by intact endothelium. The lining has evidently in all examples been deposited between the endothelium and the remnants of media. Several veins contain also red thrombus. Leucocytes extend from the veins into the surrounding tissue. The inner part of the necrosed jejunum contains numerous Gram-positive cocci and bacilli.

The *spleen* was small and firm and showed a normal pattern on section. In a microscopic section a large vein contains recent red thrombus, and two arteries are occluded by canalized fibromuscular and elastic tissue.

*Kidneys.* The surface of the right kidney was pitted by one large and several small fibrotic scars. In microscopic sections the large scar is a fibrosed infarct, while the others are areas of dense ischaemic fibrosis. At the apex of the infarct an interlobular artery shows absence of media and occlusion by canalized musculo-elastic tissue. The left kidney shows only albuminous degeneration of the first convoluted tubules and fatty degeneration of the second.

*Left suprarenal body, body of pancreas, and right optic thalamus.* In these no microscopic evidence of recent or old arterial necrosis could be found.

*Necropsy diagnosis.* Purulent broncho-pneumonia. Haemorrhagic necrosis of jejunum due to acute necrosis of arteries ('necrotizing arteritis'). Heart failure. Aneurysm of fibrotic apex of left ventricle; recent, granulating and fibrosed focal rheumatic necroses throughout myocardium; recent and old acute necrosis of myocardial arteries. Active and healed rheumatic endocarditis of mitral and aortic valves. Canalized occlusion of arteries, probably following acute necrosis, in spleen and right kidney. Multiple fibrosed infarcts in right kidney. Recent infarct in lower lobe of right lung. Moderate general atheroma: fatty streaks in coronary arteries, with no

appreciable narrowing of lumina. Confluent central congestive atrophy of hepatic lobules.

*Case 4. Male, aged 54.*

*History.* In May, 1934, sudden attack of substernal pain, radiating to the left arm, lasting two days. Nine days later, attack of aphasia, followed by syncopal attacks. He was kept in bed for two months, but subsequently developed increasing dyspnoea and oedema, for which he was admitted to hospital in October, 1934.

*Examination.* Pulse 110, regular. Arteries thickened. Blood-pressure 130/80 mm. Apex-beat heaving, 6th interspace in anterior axillary line, gallop rhythm. Pre-systolic thrill and murmur at apex. Liver enlarged. Anasarca. Ascites. Right hydrothorax. W.R. negative.

*Electrocardiogram.* Normal rhythm, low voltage *QRS* all leads, *T* flat all leads, slight *R-T* elevation.

*X-ray.* Anterior view, enlargement of heart to left with slight enlargement to right, pulmonary arc prominent, calcification of aortic knuckle. In the right oblique position, prominence of left auricle.

*Diagnosis.* Coronary occlusion. Mitral stenosis. Cardiac aneurysm.

*Course.* After discharge, in December, 1934, relapsed, and readmitted to hospital in March, 1935. There were again signs of congestive heart failure, and the blood-pressure was 125/85 mm. Died suddenly five days after admission.

*Necropsy.* Great enlargement of the left ventricle. Whole of the apex replaced by fibrous tissue and slightly aneurysmal, although not obviously bulging. Diffuse fibrosis of remainder of left ventricle. Anterior descending coronary artery occluded by an old, organized clot. Atheroma of other coronary arteries. Considerable amount of free fluid in pericardium, and old standing adhesions over the apex. Stenosis of mitral valve.

*Necropsy diagnosis.* Mitral stenosis. Coronary occlusion. Aneurysm of left ventricle.

*Case 5. Male, aged 55.*

*History.* In December, 1935, prolonged attack of severe pain across middle of chest, radiating to both arms, accompanied by vomiting. Diagnosis, coronary thrombosis. In January, 1936, epigastric pain after meals, loss of appetite, and vomiting. In November, 1936, seen by us, complaining of pain after food, vomiting, and loss of weight, but no anginal pain.

*Examination.* Pulse 84, regular. Arteries normal. Blood-pressure 105/75 mm. Apex-beat in nipple line. Area of localized, expansile, systolic pulsation palpable in 3rd left interspace, 4 in. from midline. Heart sounds of normal intensity. W.R. negative. No sign of congestive heart failure. Emaciated and anaemic. Hard mass palpable in left hypochondrium and epigastrium.

*Electrocardiogram.* Normal rhythm, large  $Q_1$ , inversion of  $T_1$ .

*X-ray.* Anterior view, heart and aorta of normal dimensions, blunting of apex, diminished apical pulsation (Plate 27, Fig. 2). In the right oblique position, marked ledging of anterior heart border with obvious bulge which exhibited systolic expansion (Plate 27, Fig. 3).

*Diagnosis.* Old coronary thrombosis. Anterior cardiac infarction. Cardiac aneurysm. Carcinoma of stomach.

*Course.* Patient became rapidly weaker and died in January, 1937. Blood-pressure fell to 80/60 mm.

*Necropsy.* Large aneurysmal sac, 8 cm. in diameter, projecting directly forwards from anterior wall of left ventricle, but not involving apex, lined by partly organized, adherent clot 5 mm. thick. The wall of the sac was formed entirely by fibrous tissue 2 mm. thick, and the pericardium overlying it was thickened and adherent. Hypertrophy of remaining ventricular muscle. Anterior descending coronary artery completely occluded and calcified in the first 2 cm. of its course. Left circumflex and right coronary arteries atheromatous and stenosed, but not occluded. Large, ragged growth of stomach, invading the transverse colon and liver and adherent to the diaphragm.

*Necropsy diagnosis.* Aneurysm of left ventricle. Occlusion of anterior descending coronary artery. Carcinoma of stomach.

*Case 6. Male, aged 56.*

*History.* In September, 1930, attended hospital with substernal pain, radiating to left shoulder, of six days duration. In November, 1930, at home, severe attack of pain all over front of body lasting for seven days. Returned to work as a presser five weeks later. Remained at work until April, 1933, when he was admitted to the London Hospital under the care of Dr. Donald Hunter, complaining of general malaise, pain in left chest, sweating, and rusty expectoration.

*Examination.* Pulse 112, regular. Arteries thickened. Blood-pressure 110/70 mm. Heaving pulsation of praecordium, visible through his bed-clothes. Apex-beat 7th interspace, in anterior axillary line, with indrawing of chest-wall below apex. Heart sounds distant. W. R. negative.

*Electrocardiogram.* Normal rhythm, left axis deviation. Inversion of  $T_1$  and  $T_2$ .

*X-ray.* Anterior view, great enlargement of heart with an enormous bulge on the left ventricle above apex, the angle between the bulge and the vascular pedicle being almost a right angle (Plate 27, Fig. 4).

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* On 28th April, 1933, a cerebral embolism occurred with aphasia and right hemiplegia. He left hospital in November, 1933, and died following a 'stroke' two years later.

*Case 7. Male, aged 67.*

*History.* In March, 1934, he had an attack diagnosed as coronary thrombosis.

*Examination* (May, 1934). Pulse 80, regular. Arteries normal. Blood-pressure 120/80 mm. Apex-beat 4th interspace, external to mid-clavicular line. Cheyne-Stokes respiration.

*Electrocardiogram.* Normal rhythm, inversion of  $T_2$  and  $T_3$ .

*Examination* (November, 1934). Apex-beat 1 in. external to mid-clavicular line, with considerable area of visible pulsation beyond the left nipple. Heart sounds distant.

*X-ray.* Anterior view, blunting of apex. In the left oblique position, the posterior heart border had a double curve, the upper bulge being formed by the aneurysmal pouch, the lower one by the left ventricle (Plate 28, Fig. 6).

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* The patient has been seen from time to time up to May, 1937, and is still living, free from anginal pain and able to walk for an hour daily. Forcible pulsation can be felt in the left 3rd and 4th interspaces, internal and external to mid-clavicular line. Later X-ray examination shows

absence of pulsation at the lower part of left heart border. The bulge of the upper part of the left ventricle is rather more obvious, and a definite incisura can be seen between the aneurysm and the apex of the heart (Plate 28, Fig. 5).

*Case 8. Male, aged 39.*

*History.* In August, 1934, severe attack of pain in epigastrium, diagnosed as gall-stone colic. In October, 1934, he collapsed in a severe attack of pain across the front of the chest, and a diagnosis of coronary thrombosis was made. He recovered, but, while at work in October, 1935, he had an attack of paroxysmal tachycardia, rate 150, lasting twelve hours. Since then subject to anginal pain on effort.

*Examination* (October, 1935). Pulse regular. Blood-pressure 120/80 mm. Apex-beat, 5th interspace,  $\frac{1}{2}$  in. external to mid-clavicular line, gallop rhythm. W. R. negative. No signs of congestive heart failure.

*Electrocardiogram.* Normal rhythm, left axis deviation, QRS widened all leads, elevation of  $R-T_1$ , inversion of  $T_1$ .

*X-ray* (January, 1936). Anterior view, gross enlargement of heart to left, with blunting of apex and absence of apical pulsation.

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* After a rest, he obtained work as a night-watchman, which he is still able to do in 1937. When last seen, the apex-beat was diffuse and in the anterior axillary line, while an X-ray showed slight systolic expansion of the left ventricular bulge.

*Case 9. Male, aged 30.*

*History.* In 1929, when aged 23, coronary thrombosis. Since then, attacks of palpitation of sudden onset, after exertion, lasting half an hour. In 1932, an electrocardiogram, taken during an attack, showed ventricular tachycardia.

*Examination* (October, 1936). Pulse 80, regular. Blood-pressure 130/75 mm. Apex-beat, 5th interspace, 1 in. external to mid-clavicular line. Heart sounds, first sound accentuated, systolic murmur and reduplicated second sound at apex. W. R. negative. No signs of congestive heart failure.

*Electrocardiogram.* (a) Normal rhythm, left axis deviation, prominence of  $Q_1$ , inversion of  $T$  in all leads.

(b) Ventricular tachycardia, rate 145.

*X-ray.* (a) 1932. Anterior; an obvious bulge on the upper half of the left ventricular contour.

(b) 1936. Anterior view, the bulge on the left ventricular contour is larger and surrounded by a linear shadow of calcification, which can be traced some distance within the heart shadow at the upper and lower limits of the bulge (Plate 28, Fig. 7). In the right oblique position, the aneurysm, encircled by calcification, bulges forwards, causing ledging of the anterior border (Plate 28, Fig. 8). In the left oblique position, the aneurysm, again outlined by calcification, lies within the heart shadow.

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle. Paroxysmal ventricular tachycardia.

*Course.* While in hospital at this time, a paroxysm of ventricular tachycardia occurred, lasting fifty-two hours. In March, 1937, still having attacks of tachycardia lasting 2-6 hours, and pain near the apex-beat not specially related to effort. Able to walk three miles.

*Electrocardiogram* (November, 1937).  $T_3$  now upright, otherwise no change.

*Case 10.* Male, aged 59.

*History.* Two weeks before examination, onset of angina of effort, culminating in a prolonged anginal seizure lasting twelve hours and typical of coronary thrombosis.

*Examination* (June, 1932). Pulse 110, regular. Blood-pressure 130/90 mm., falling to 95/65 mm. Heart sounds distant; pericardial friction at apex. Temperature 100° F. W. R. negative.

*Electrocardiogram* (1933). Normal rhythm, prominence of  $Q_1$ , elevation of  $R-T_1$ , inversion of  $T_1$ .

*X-ray.* (a) *March, 1933.* Anterior view, slight enlargement of heart, with shelving of left border and blunting of apex. In the right oblique position, ledging of the anterior heart border.

(b) *1937.* Anterior view, larger bulge of left border above the apex (Plate 31, Fig. 16).

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* In March, 1933, he was able to walk three miles. In 1937, writes that he has continued well.

*Case 11.* Male, aged 74.

*History.* For seven months increasing dyspnoea and constant pain below left breast.

*Examination* (September, 1929). Pulse 100, regular. Arteries sclerosed and tortuous. Blood-pressure 120/80 mm. Apex-beat very forcible, 6th interspace, in anterior axillary line. Heart sounds distant. Left hydrothorax, and congestive heart failure.

*Electrocardiogram.* Normal rhythm, *QRS* widened and notched in all leads, prominence of  $Q_1$ , slight elevation of  $R-T_1$ , inversion of  $T_1$ .

*X-ray.* Anterior view, gross enlargement of heart to left, with obvious bulge on upper part of left ventricular border (Plate 31, Fig. 17). Abnormal pulsation of left border above this bulge, but not in it.

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* Improved and left hospital. Continued to attend as an outpatient with slight heart failure and epigastric pain. November, 1930, blood-pressure 125/90 mm. Heart sounds distant. Died suddenly at home a few days later.

*Case 12.* Male, aged 58.

*History.* Admitted during an attack of severe substernal pain, radiating to both arms, which had begun 2½ hours before. Pain accompanied by vomiting and sweating.

*Examination* (December, 1934). Pulse 110, regular. Blood-pressure 145/90 mm. Apex-beat impalpable. Heart sounds distant. No oedema.

*Electrocardiogram.* Normal rhythm, low voltage *QRS* all leads, prominence of  $Q_1$ , elevation of  $R-T_1$ .

*X-ray* (February, 1935). Anterior view, angulation of left heart contour with blunting of apex. Heart not otherwise appreciably enlarged. In the right oblique position, ledging of anterior border, where the aneurysm bulges forwards (Plate 31, Fig. 15).

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Course.* While in hospital, several anginal attacks and one attack of biliary colic; later, embolism of left middle cerebral artery. He could not be traced after discharge from a municipal hospital in November, 1935.

*Case 13.* Male, aged 70.

*History.* In October, 1936, attack of severe epigastric pain, diagnosed as coronary thrombosis. Recurrence of pain two weeks later. In December, 1936, a second attack of coronary thrombosis. In January, 1937, blood-pressure 115/70 mm.; pericardial friction; electrocardiogram, deviation of  $R-T_1$ , inversion of  $T_1$  and  $T_2$ .

*Examination* (March, 1937). Pulse 75, regular. Arteries normal. Blood-pressure 140/85 mm. Apex-beat not palpable. Heart sounds clear.

*Electrocardiogram.* Normal rhythm, inversion of  $T_1$ , elevation of  $R-T$  and inversion of  $T$  in Lead IV ( $R$ ).

*X-ray.* Anterior view, bulging of left ventricular contour above apex, showing expansile pulsation (Plate 29, Fig. 9). In the right oblique position, marked ledging of anterior contour (Plate 29, Fig. 10).

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Case 14.* Male, aged 59.

*History.* In 1933, series of brief anginal attacks, unrelated to effort, for two weeks. In 1935, recurrence of these attacks following exercise. Had to give up work three months before examination, owing to dyspnoea.

*Examination* (March, 1937). Pulse 72, regular. Blood-pressure 135/90 mm. Apex-beat in anterior axillary line. Whole left chest rises and falls with each heart-beat. Tenderness over apex. Heart sounds clear. W.R. negative. Slight enlargement of liver, but no oedema.

*Electrocardiogram.* Normal rhythm, elevation of  $R-T_1$ , inversion of  $T_1$ .

*X-ray.* Anterior view, gross enlargement to left, with ledging of left border, and abnormal pulsation at apex (Plate 29, Fig. 11). In the right oblique position, bulging of anterior heart border which is adherent to chest wall.

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

*Case 15.* Male, aged 62.

*History.* In March, 1936, he was in hospital with coronary thrombosis, when the systolic blood-pressure fell below 100 mm., and he had acute pulmonary oedema. Electrocardiogram showed  $R-T$  deviation and later inversion of  $T_1$  and  $T_2$ . He improved, but in October, 1936, was again in hospital with congestive heart failure, which gradually responded to treatment. When seen by us in December, 1937, he could walk slowly for half an hour, but was breathless on slight exertion.

*Examination* (December, 1937). Pulse 60, regular. Blood-pressure 125/90 mm. Apex-beat, in 6th interspace in anterior axillary line, forcible. Heart sounds distant. Liver enlarged and slight oedema of legs.

*Electrocardiogram.* Normal rhythm, widening of  $QRS$  in all leads, prominent  $Q_1$ , inversion of  $T_1$ ,  $P-R$  exceeds 0.2 sec., suggestive of left bundle-branch block.

*X-ray* (October, 1937). Anterior view, the heart is greatly enlarged to the left, with an obvious bulge on the upper half of the left ventricular contour. This bulge produces ledging below the left hilum, so that the upper border of the left ventricle runs horizontally outwards (Plate 29, Fig. 12). In the right oblique position, the aneurysmal bulge is seen projecting forward and obliterating the lower part of the anterior light space which fails to illuminate on deep inspiration. The upper border of the bulge causes ledging of the anterior heart contour (Plate 30, Fig. 13). In the left oblique position, the outline of the left ventricle is hemispherical.

*Diagnosis.* Coronary occlusion. Aneurysm of left ventricle.

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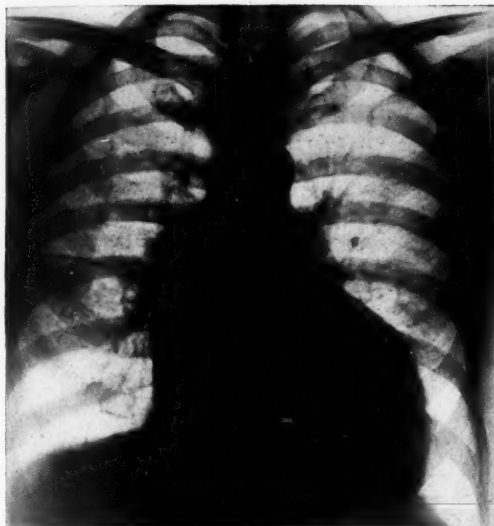


FIG. 1. Case 2. Anterior teleradiograph showing enlargement of heart to left, slight angulation of left border within which is linear calcification. P.M. control



FIG. 2. Case 5. Anterior teleradiograph showing heart of normal size and only slight angulation of left border (see Fig. 3). P.M. control



FIG. 3. Case 5. Right oblique teleradiograph showing aneurysmal bulge of anterior heart contour with 'ledging'. Expansile pulsation of sac visible on screening. P.M. control

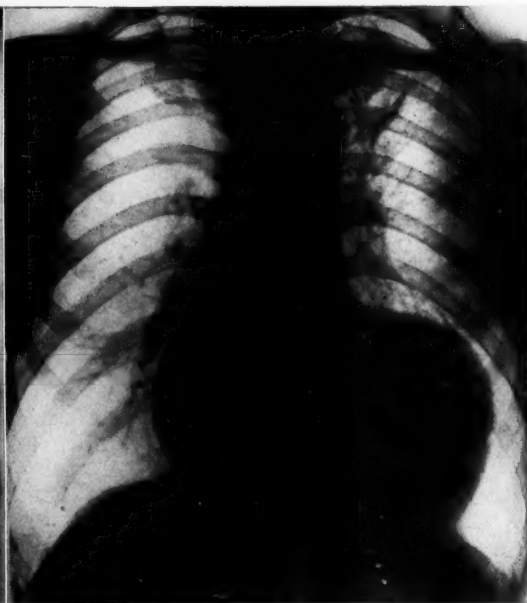


FIG. 4. Case 6. Anterior teleradiograph showing large aneurysmal bulge of upper half of left ventricle and 'squaring' of heart



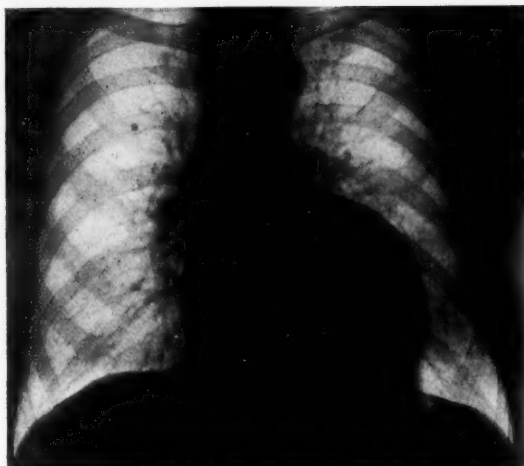


FIG. 5. Case 7. Anterior teleradiograph showing posterior aneurysm projecting above and beyond the apical outline



FIG. 6. Case 7. Left oblique teleradiograph showing a double curve on posterior heart border. The upper curve which displaces the oesophagus is formed by the aneurysm, the lower curve by the left ventricle proper

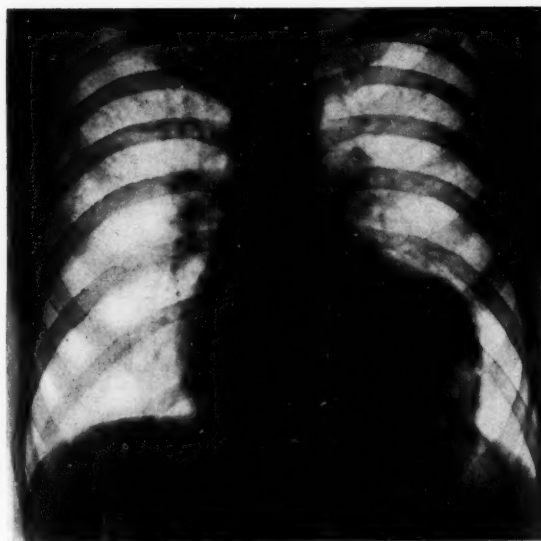


FIG. 7. Case 9. Anterior teleradiograph showing 'squaring' of heart due to large aneurysm of left ventricle; the aneurysm is lined with calcification

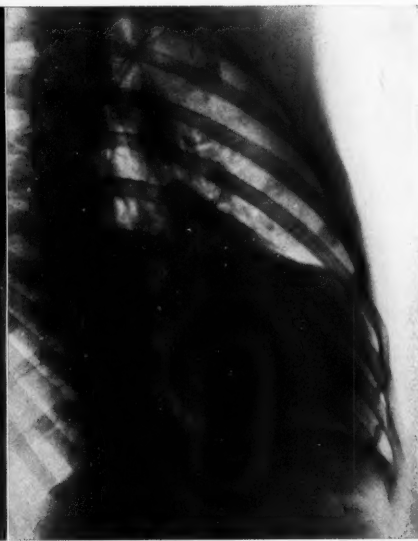


FIG. 8. Case 9. Right oblique teleradiograph showing ledging of anterior heart contour due to calcified aneurysm



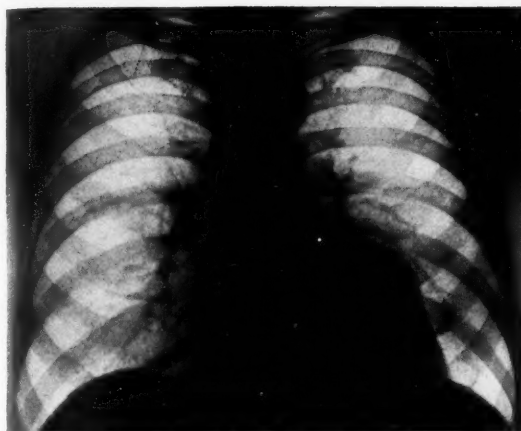


FIG. 9. Case 13. Anterior teleradiograph showing angulation of left heart border. Expansile pulsation of aneurysm visible on screening



FIG. 10. Case 13. Right oblique teleradiograph showing aneurysmal bulge on anterior heart border with typical ledging

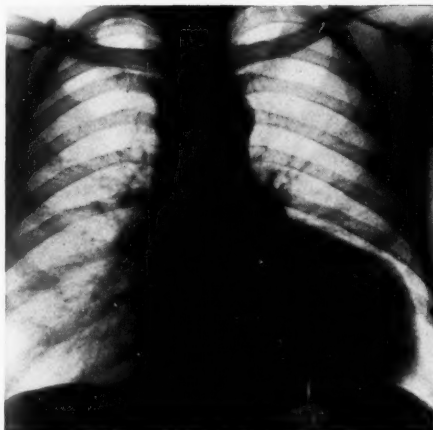


FIG. 11. Case 14. Anterior teleradiograph showing elongation of heart and angulation of left border



FIG. 12. Case 15. Anterior teleradiograph showing great enlargement of heart to left (elongation), with 'squaring' of left heart border





FIG. 13. Case 15. Right oblique teleradiograph (in deep inspiration) showing aneurysmal bulge of anterior surface of heart, with ledging



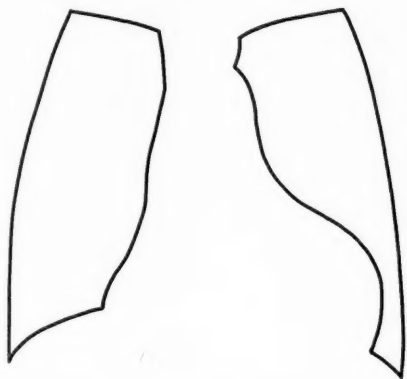


FIG. 14. Case 1. Cardiac aneurysm. P.M. control. Outline of teleradiograph showing gross enlargement of heart to left and blunting of apex

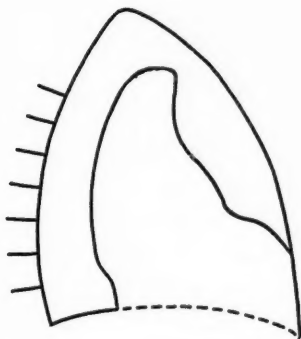


FIG. 15. Case 12. Outline of right oblique teleradiograph showing aneurysmal bulge with ledging of anterior heart border

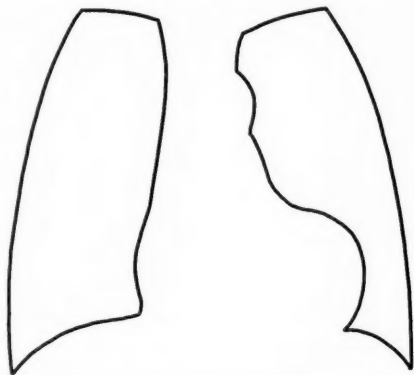


FIG. 16. Case 10. Outline of teleradiograph showing enlargement of heart to left and bulging of left border

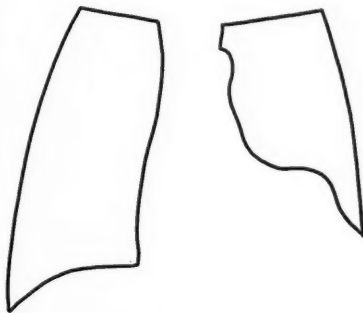


FIG. 17. Case 11. Outline of teleradiograph showing gross enlargement of heart to left, with localized aneurysmal bulge of left ventricle

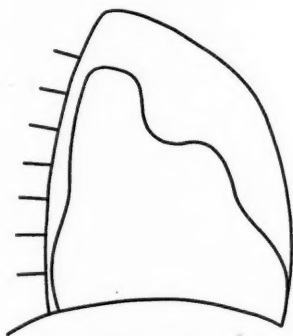
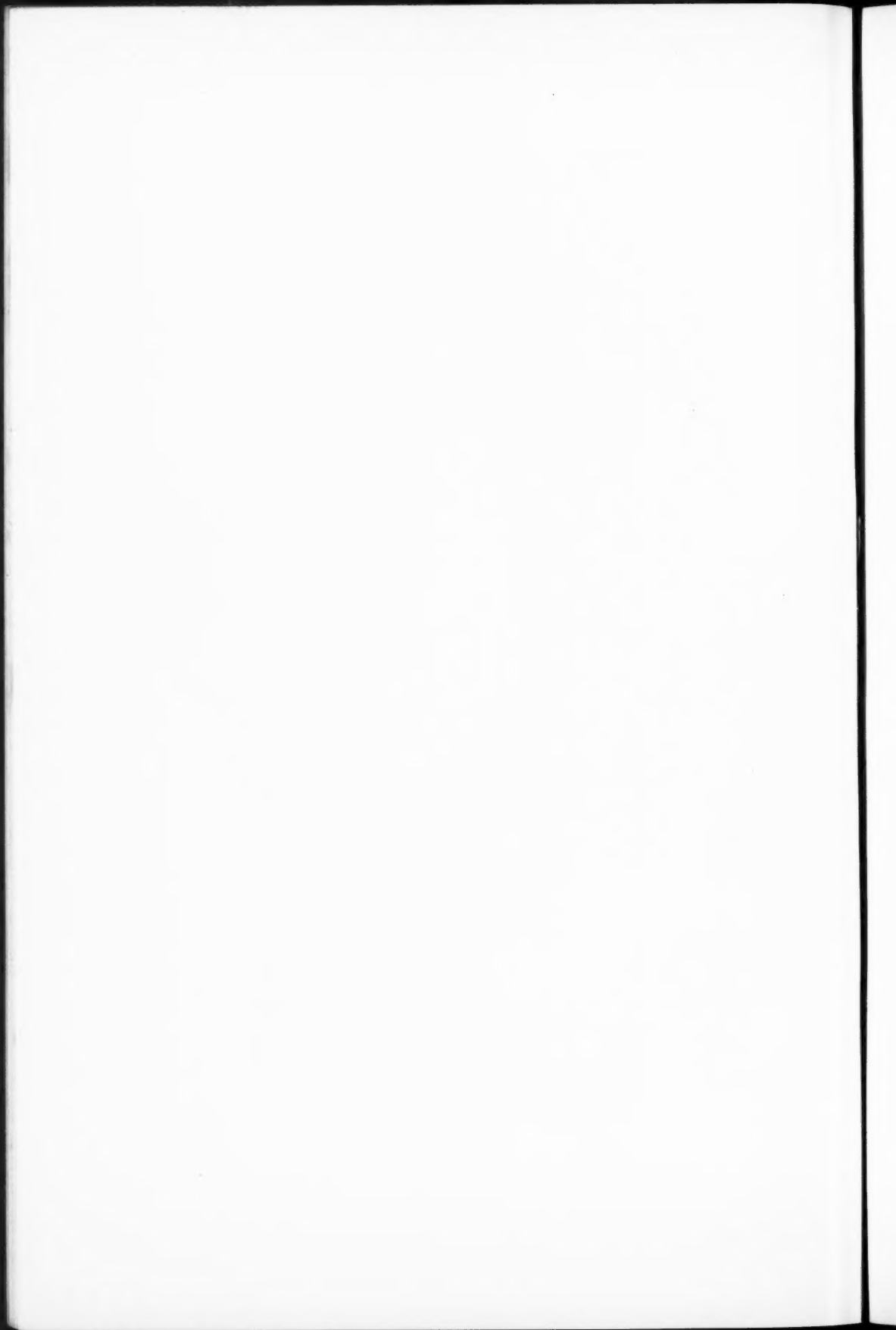


FIG. 18. Aneurysm of root of aorta (sinus of Valsalva). P.M. control. Outline of right oblique teleradiograph to show ledging which simulates that of cardiac aneurysm



THE GENETICS OF TRANSPOSITION OF THE VISCERA<sup>1</sup>

By E. A. COCKAYNE

BEFORE proceeding to my main theme, the Genetics of Transposition of the Viscera, I will deal briefly with its nature and causation. Many of the older authors thought that all the organs of the body were transposed to form a mirror image of the normal, and in support of this they said that nearly all those with situs inversus were left-handed. Actually left-handedness is no commoner in those with transposed viscera than in normal people. Taking 115 cases without selection from the literature and from my series, I find 106 right-handed, seven left-handed, and two ambidextrous, and since the incidence of left-handedness in Europe varies from 1 to 8 per cent., it is clear that the brain centre, which governs right-handedness, is not transposed.

In early embryonic life the thoracic and abdominal viscera are at first disposed regularly about the median plane of the body. The heart begins as a median tube with the aortic arches symmetrically arranged on each side, the right and left portions of the liver are disposed symmetrically to the median axis, the stomach is a straight tube, the intestinal loop and the hind gut are median, while the pancreas begins as a series of dorsal and ventral buds symmetrically disposed.

In the normal course of development dextral rotation of the viscera takes place, so that the bilateral symmetry gives way to spiral symmetry. In transposition of the viscera rotation occurs, but in the reverse direction, with the formation of a sinistral instead of a dextral spiral, and in both cases the spiral approaches the logarithmic type. Lewis (1923) has shown this clearly in his note on 'Symmetry as a Factor in the Evolution of Plants and Animals', and points out how commonly logarithmic and Archimedean spirals occur in nature. Bateson (1913) in his book *Problems of Genetics*, referring to monozygotic twins, wrote, 'If anyone could show how it is that neither of a pair of twins has transposition of the viscera the whole mystery of division would, I expect, be greatly illuminated.' I hope in this paper to give the solution of Bateson's problem.

Many theories have been put forward to explain the causation of transposition of the thoracic and abdominal organs, but I need refer only to one of them. Foerster (1861) observed that in the majority of double monsters, particularly in thoracopagi and ischiopagi, one had complete or partial transposition of the viscera, and he advanced the theory that in cases of transposition in separate individuals there has been monozygotic twinning with the subsequent death and absorption of the twin with normal viscera. If this

<sup>1</sup> Received March 31, 1938.

were so there should be many pairs of twins, one with normal and the other with transposed viscera, but this is not the case. Dubreuil-Chambardel (1927) has indeed recorded a pair, one with a hare-lip on the right, the other with a hare-lip on the left, one with normal, the other with reversed viscera, but I do not know of any other authentic example.

Transposition of the viscera in one of conjoined twins appears to be caused in a different way from transposition in single individuals, and Bateson (1913) is probably correct in believing that in the former case it is an attempt to produce symmetry, though the mechanism by which this is brought about is still unexplained.

Very few writers even mention the possibility that the condition is inherited, and most of those who do so dismiss it as improbable. Matisson (1933) in a recent paper on its heredity says a weighty argument against the theory of inheritance is that it so rarely occurs in members of two successive generations. His objection would apply to a dominant, but not to a recessive character. According to a citation in an Italian paper, Dessylla and Monticelli (1931) formulated the hypothesis that it is a recessive character, but as there is no copy of their paper in this country, I do not know on what grounds they based their opinion. Long before I found this reference I had suspected that it was a recessive mutation, and I now offer evidence that it is determined genetically and is inherited as a recessive trait.

*Recognition of a rare recessive character.* A rare recessive character can be recognized by its distribution in the families in which it occurs, by the ratio of children with it to normal children in the same fraternity, and by the rate of consanguinity of the parents, one or more of whose children have it. When homozygous recessives are rare, their parents will in an overwhelming majority of instances be normal, and in large fraternities it is to be expected that more than one child will exhibit the recessive character. The children and the half-brothers and half-sisters of those with the recessive character will almost invariably be normal, but ascendants and collaterals will occasionally exhibit it.

Applying these criteria to complete transposition of the viscera, it is found that, scattered through medical literature, there are a number of well authenticated examples of its familial incidence. Five sibships with three affected members have been recorded—three brothers by Liotta (1927), Ōshima (1929), and Carpenter, two brothers and a sister by Fröhlich (1922), and a brother and two sisters by Feldman (1935). There are 16 examples of fraternities in which two sibs are affected, and to these I can add two more from my series. Reid (1909), Lowenthal (1909), Leroux, Labbé, and Barret (1912), and Ochsenius (1920) have recorded the condition in two brothers, Gall and Woolf (1934), Mittelbach (1930), Günther (1923), and Müller-Pollak (1929) in two sisters, and Hofmann (1926), Bianchi (1927), Neuhof (1913), Rogi (1880), Brimblecombe (1920), Cürschmann (1919), Cahan (1925), and Manson (1935) in a brother and sister, and in my series there are two examples of a brother and sister with the anomaly. I have been unable to refer to three additional

cases of its familial incidence, which are said to have been recorded by Baumann, Peters, and Samoiloff. In all these familial cases the parents were either found to be normal or were stated to be normal.

*Cases of parent and child with transposition.* The child of an individual manifesting a recessive character can be affected only when his parent, who is homozygous, marries a heterozygote (a carrier); and the rarer the character the less often will this happen. Matisson (1933) saw a mother and daughter, both of whom were proved by clinical examination and by skiagram to have complete transposition of the viscera, and Meyer and Hürlimann (1916) saw a man with the anomaly, whose son is said to have had it also. In Matisson's case there was no blood relationship between the parents of either patient, but in the other it is not stated whether they were or were not consanguineous. As far as I am aware, there are only these two reliable records of the occurrence of transposition of the viscera in a parent and child. On the other hand, there are a large number of instances in which both parents were examined and found to be normal, and a much larger number in which they themselves or their children said they were normal. There are also a large number of records proving that the children of individuals with the condition are all normal.

*Half-brothers and half-sisters.* The parents of a person with a recessive character both transmit it and must both be heterozygous, but in the case of a rare character, if one of them marries again, it is most unlikely that he will marry another heterozygote, unless he marries a blood relation of his own or of his wife, such as his deceased wife's sister. Half-brothers and half-sisters are therefore very unlikely to show the recessive character. There are many examples in the literature in which half-brothers and half-sisters were normal, but none in which they had complete transposition of the viscera.

*Ascendants and collaterals.* Recessive characters occasionally appear in ascendants and collaterals, often as a result of consanguineous marriages or intermarriage between the same two families, but sometimes by chance. Randolph (1905) has recorded the case of a boy and his maternal grandfather, both of whom had complete transposition. Katzmann (1933) found it in female cousins with the same surname, but does not say whether their fathers or grandfathers were brothers, or whether the marriages were consanguineous. In my series there are two examples of its occurrence in an uncle and nephew, the son of a brother and the son of a sister respectively. None of the marriages were consanguineous and in the second the marriages were not between members of the same two families. Both cases, however, occurred in a small village or town. Thus in every respect transposition of the viscera behaves like a recessive character in its distribution within a family.

*Monozygotic twins.* If a condition is inherited either as a dominant or a recessive, it should affect both members of a pair of monozygotic twins, or neither. Araki (1935) has recorded transposition of the viscera in both members of a pair of Japanese monozygotic twins. Pezzi and Carugati (1924) examined a pair of male twins and proved that both had the condition, but

made no definite statement that they were monozygotic. Boccia and Maglione (1927) record another pair of Italian male twins and say that, as they were both temperamentally and morphologically alike, they were probably monozygotic. Reinhardt (1912) not only gives proof that both members of a pair of German male twins had complete transposition of the viscera, but says they were monozygotic and were members of a family in which a tendency to twinning was inherited. In my series there is one example of a pair of male twins, both with transposition of the viscera. Both had pulmonary tuberculosis, of which one had died, so that no proof that they were monozygotic could be obtained beyond the statement of the survivor, that they were often mistaken for one another by friends and acquaintances and sometimes even by their mother. There appears to be only one record of its occurrence in one member and not in the other, and to this I will refer later. It has been found in one member of a pair of dizygotic twins, but I know of no authentic case in which it has been found in both.

*The ratio of children with a recessive character to the normal children of the same fraternity. Exact quantitative analysis.* When two people heterozygous for a recessive character marry, the ratio of affected to normal children should be 1 : 3, but actually in man the ratio is usually found to lie between 1 : 1.5 and 1 : 2. There are two reasons for this. Since human families are small, many heterozygous parents will have no affected children, but statistically these will be compensated for by other families, in which the proportion of affected children is in excess of expectation. The latter will be included in the count, but the former will be omitted. There will, for example, be a number of sibships consisting of an only child with the anomaly, but there will be three times as many, in which the only child is normal, though the parents are heterozygous and therefore potential parents of an affected child. Heterozygous parents cannot be recognized unless they have at least one child with the anomaly, and so the actual ratio is found to be more than 1 : 3. Correction for this can, however, be made by using Hogben's (1931) or Haldane's (1932) formula, provided the fraternities are numerous and unselected.

The second reason why the actual ratio found differs from that expected is that fraternities containing more than one affected member are more likely to be recorded than those in which only one is affected. Both sources of error occur with transposition of the viscera, but there is still greater difficulty, that of obtaining enough reliable fraternities for exact statistical analysis. The anomaly is one which cannot be recognized by relatives and may even be overlooked on clinical examination. Since it very rarely happens that every member of the larger fraternities can be examined, these will appear to have fewer affected members than is really the case, if those not examined are accepted by hearsay evidence as normal. The very small fraternities, on the other hand, are much more reliable, in that all the children are likely to be examined. If, therefore, only those fraternities in which every child has been examined are subjected to analysis, the majority will be small ones, and the ratio of affected to normal members will be too high. In fraternities

known to contain more than one affected member, the remainder are more likely to be examined than in those of which only one member is known to be affected, and this raises the ratio still more. Correction for this is not possible either by Hogben's (1931) or Haldane's (1932) formula. My own series of 50 unpublished fraternities suffers from the same defect as those extracted from medical periodicals, and only 52 derived from both sources are reliable enough to be submitted to statistical analysis. These are shown in the following table, and the ratio of affected to normal sibs is 1:1.7.

TABLE I

*Reliable Sibships (all Sibs Examined)*

Number in sibship.	Number of sibships.	Affected.	Normal.
1	5	5	—
2	20	21	19
3	13	15	24
4	9	11	25
5	3	4	11
6	1	1	5
7	1	1	6
Totals	52	58	90

Taking all the 119 available fraternities and counting all those not examined as normal, but omitting those who died in early infancy, as shown in the second table, the ratio is 1:2.9, and, including those who died in infancy, it is 1:3.1.

TABLE II

*All Sibships, Omitting those who Died under 1 Year of Age*

Number in sibship.	Number of sibships.	Affected.	Normal.
1	5	5	—
2	24	26	22
3	22	26	40
4	21	23	61
5	12	13	47
6	11	14	52
7	10	14	56
8	3	3	21
9	5	5	40
10	2	2	18
11	1	1	10
12	1	3	9
13	1	1	12
15	1	1	14
Totals	119	137	402

The first figure, owing to the selection of small fraternities and those with more than one affected member, gives too high a proportion of affected sibs, and the second, owing to the counting of all those not examined as normal, gives too low a proportion. The middle figure comes very close to the exact mendelian ratio, but this ratio is not expected, because the children of heterozygotes who have no abnormal child, are not included. Though exact analysis

is impossible, it is clear that the ratio approximates to that expected of a recessive condition.

*Consanguinity of parents.* A high rate of consanguinity between parents, one or more of whose children manifest a rare anomaly, is the best criterion that it is recessive. The incidence of consanguineous marriages is known only in the case of marriages between first cousins, and even the frequency of these is unevenly distributed in different sections of the community. It is, for example, higher amongst Jews and Quakers than amongst the general population of the same areas, and it is also higher in small isolated communities than in large towns. Amongst hospital patients in large towns in England the frequency lies between 0.6 and 0.9 per cent., and for the whole country must be under 1 per cent. Since the percentage of first-cousin marriages giving rise to a recessive character increases with the increasing rarity of the character, it is important to know the incidence of complete transposition of the viscera, in order to see if the percentage ascertained agrees with that expected. Unfortunately the figures given by different authors show a wide discrepancy between the highest and the lowest. Those given by radiologists, 1 : 1,400 (Le Wald, 1925) and 26 : 39,000 (Reinberg and Mandelstam, 1928), owing to selection show an incidence which is far too high and can be ignored. Those based on clinical examination are probably too low (20 : 476,402) and give an incidence of 1 : 23,800. My figures taken from school children in the London County Council area born in 1924 and 1925 are 4 : 96,504 and in North Lancashire 1 : 1,173, giving an incidence of 1 : 19,500. Figures derived from German post-mortem examinations (14 : 124,830) give an incidence of 1 : 8,900. Lenz (1919) gives a formula for calculating the rarity of a recessive from the percentage of first-cousin marriages giving rise to it based on the assumption that the frequency of first-cousin marriages in the general population is 1 per cent. If the frequency of transposition of the viscera lies between 1 : 9,000 and 1 : 24,000 the percentage of first-cousin marriages giving rise to one or more children with it lies between five and nine. Unfortunately very few of the authors who have published cases mention whether the parents were or were not first cousins, but of those fraternities, about which this information is given, the parents were first cousins in two and unrelated in 14. These fraternities however cannot be accepted as a random sample.

My own series collected by the courtesy of many medical men in this country and overseas, in Canada, South Africa, and Australia, and by the Medical Officers of the London County Council through the Medical Research Council, is free from error due to selection, and by the accumulation of further data I hope in time to arrive at an accurate estimate of the percentage. Of 53 fraternities, six had parents who were first cousins. On so small a series it is unsafe to base a percentage, but if the ratio held good for a longer series, 11 per cent. of fraternities would arise from first-cousin marriages and this would correspond with a frequency of 1 : 40,000. Such a percentage is higher than that expected, but even a percentage of only six

would be a convincing proof that the condition is determined by a single recessive gene. Thus complete transposition of the viscera agrees with what is expected of a rare recessive character in its familial incidence and general distribution within a family, in its occurrence in both members of a pair of monozygotic twins whose parents are normal, in the high percentage of first-cousin marriages that give rise to it, and, so far as can be ascertained, in the ratio of affected to normal children in fraternities.

Haldane (1936) has recently shown that some recessive characters, such as xeroderma pigmentosum, which conform with these criteria, are not autosomal, but are partially sex-linked and are determined by genes in a part of the X-chromosome, which frequently crosses over to the corresponding part of the Y-chromosome. They can be recognized by the fact that in large sibships there is a strong tendency for all or most of those affected to be of the same sex, male if the gene is in the father's Y- and female if it is in the father's X-chromosome. In the familial cases of transposition of the viscera those affected are all male in seven sibships, all female in four, and both male and female in 12. The data are scanty, but, so far as they go, they point to the condition being autosomal and not partially sex-linked.

This then is the explanation of Bateson's (1913) problem. Both members of a pair of monozygotic twins are heterozygous or homozygous for the gene which determines dextral rotation, or they are homozygous for the gene which determines sinistral rotation, and are therefore both normal or both have their viscera transposed. The real problem is to explain the exceptional case described by Dubreuil-Chambardel (1927), in which one twin had the viscera rotated normally and the other had them reversed. There are at least two possible explanations, loss of the whole or part of an autosome (one member of a pair of corresponding chromosomes), or somatic mutation. In both cases one must assume that the zygote was heterozygous. On the first hypothesis, at the first cleavage of the zygote the whole chromosome, or that part of it which carried the dominant gene for normal rotation, was lost to the cell from which the tissues of the twin with transposed viscera were derived, but not to the cell from which the tissues of the normal twin were derived. On the second hypothesis, just after the first cleavage the dominant gene for normal rotation mutated in the cell from which one twin arose, making it homozygous for sinistral rotation, but no mutation occurred in the other. The mutation would be the same as that by which transposition has arisen from time to time, but instead of taking place in a germ cell it took place in a somatic cell.

Although I believe I have brought forward the first proof that complete transposition of the viscera is determined by a recessive autosomal gene, a possibility foreshadowed by Dessylla and Monticelli (1931), it does not explain how the gene causes inverse rotation. The experimental work of Spemann (1906) and Pressler (1911) on *Bombinator* and other amphibians throws some light on this. In the neurula stage a square piece of medullary plate, together with the roof of the primitive gut lying under it, was cut out

and replaced in the reverse position, so that its anterior part was directed posteriorly and its left side became its right side. From these embryos tadpoles were reared, many of which had complete transposition of the viscera. The work of Spemann and other embryologists has shown that all stages of embryonic development depend upon the stimulus of an active evocator on competent tissue, tissue in a receptive condition, and it has shown further that the evocator is a chemical substance allied to the sterols. The experiment on *Bombinator* seems to indicate that for the production of a normal spiral the tissue at a certain point to one side of the midline becomes competent and the corresponding point on the other side remains inert, or, as appears more likely, active evocator is produced at a definite point to one side of the median line. When the competent tissue or active evocator is transferred to the opposite side a sinistral spiral is formed and as a result the viscera are transposed in the adult.

It seems reasonable to suggest that the action of the gene which determines inverse rotation is either to cause competence of tissue or to liberate active evocator on the opposite side of the body to the usual one. This, though it only takes us a step farther back, would reconcile the experimental work of the embryologist with the genetical explanation which I have brought forward. That a gene can cause rotation has been proved in the case of *Drosophila melanogaster*. In this fly there is a mutant, 'rotated abdomen', in which the tip of the abdomen is rotated to the left, i.e. counter-clockwise, and Sumner and Huestis (1921) have shown that it is determined by a recessive gene in the third chromosome. Another mutant, 'abdomen rotatum', with clockwise rotation of the tip of the abdomen and partial sterility has been studied by Beliajeff (1931), who found it to be recessive, but due to a gene located in the fourth chromosome. In 1934 Nichols found a third mutant, 'abdomen rotatum 2', in which the rotation, generally counter-clockwise, is even greater, and proved that it is recessive to 'abdomen rotatum' with the gene in the fourth chromosome. There is also a recessive mutant, 'parted', with hairs on the thorax parted, wings spread, and the penis rotated through 180°, described by Morgan, Bridges, and Sturtevant (1925). It has since been lost, but there was probably a reversal of the normal rotation. Sinistral rotation in the water-snail, *Limnaea peregra*, has been proved by Boycott, Diver, Garstang, and Turner (1930) to be recessive to the normal dextral rotation, but as the twist is due to the cytoplasmic architecture and determined by the first division of the egg, the expression of the character is delayed for a generation. Diver and Andersson-Kottö (1938) have shown that in some lines there are modifying genes that tend to prevent sinistral rotation and that they also lead to increased embryonic mortality and to the production of monsters.

Once the genetic basis of transposition of the viscera is established, other points of interest arise. In the case of most, if not all, recessive abnormalities in man there is an excess of affected males, for which no satisfactory explanation has been offered. In the case of complete transposition of the

viscera, published cases show a great excess of males. Küchenmeister (1883) in 152 found 54 per cent. males, 29 per cent. females, and 17 per cent. of un-stated sex. Martinotti (1889) in 191 found 123 males and 68 females, and of unselected cases published during the last ten years, 65 were male and 58 female. Since it causes no symptoms, males are more likely to be discovered in the routine examination of recruits, in examination for life insurance, and before entry into the police force, the civil service, or other occupations.

My series is to a great extent free from this source of error, for most of those included were examined on account of illness or a congenital malformation. The ratio of males to females is 32 : 27. The true preponderance of males is probably less than the published figures show.

It has been found that in some human abnormalities those children who are born last are most prone to suffer, but this does not appear to be the case with transposition of the viscera (first child 17, second 19, third 18, fourth 9, fifth 7, sixth 4, seventh 1, eighth 2, ninth 2, eleventh 2, fifteenth 1).

*Racial incidence.* It is probable that the condition is of world-wide distribution, though I can find no record in any Australoid race. It has been found in Norwegian, Swedish, Danish, German, Dutch, British, French, Russian, Italian, Spanish, and Portuguese, in the white inhabitants of the Argentine, Peru, Chili, and Brazil, and in Hungarian, Rumanian, Czechoslovak, Hindu, Bengali, Arab, and Jew. Amongst these the Nordic, Alpine, and Mediterranean races must be represented. Amongst Mongoloids, Taku Komai (1934) says that there are a hundred records in the Japanese literature, there are a few in Chinese, and it has occurred in a Siamese, a Tartar, and a Filipino. In Negroid races it has been found invarious parts of Africa, and in negroes in North and South America. Nothing is known of its relative frequency in the different races.

*Is it harmless or is it disadvantageous?* In the majority of cases, transposition of the viscera is no disability, and at first sight there appears to be no reason why it should not be as common as the normal condition, for, when there is no selective advantage or disadvantage between a dominant and a recessive, they may occur in any proportion in a population and remain in equilibrium. Schulz (1930), however, says that the majority are born dead or die in early childhood, and with this view Günther (1923) agrees, but I have been unable to refer to the former paper, and in the latter no evidence is brought forward to support the statement. The fact that very few still-births and miscarriages are reported in the complete fraternities is against it.

Apart from these statements, there appears to be some evidence that congenital malformations are more liable to occur in those with transposition, and, if so, the gene must be regarded as disadvantageous, though it is harmless to those who escape this risk. Looking through the literature one is struck by the number of records of its association with congenital morbus cordis. I have found forty instances of this association, and in some of

them another malformation was also present. The commonest cardiac lesion is pulmonary stenosis with a patent interventricular septum, Fallot's tetralogy, of which there are eleven almost certain and four probable examples. In the remainder, many of which were examined *post mortem*, almost all the known cardiac malformations are represented. Other malformations have also occurred, absence of the spleen in three cases, multiple spleens, imperforate anus in three cases, atresia of the duodenum, persistent Meckel's diverticulum, absence of the appendix, horseshoe kidney, single kidney, polycystic kidneys, malformation of the oesophagus and urethra, absence of one ovary, talipes equino-varus, and hydrocephalus and spina bifida. It has also been found with microphthalmos, deaf-mutism, with gross facial asymmetry and malformation of a pinna, with neurofibromatosis, and in a cretin, a midget, and a mongol. Some of these occurrences may be accidental, but others, especially those of malformations of the viscera, are probably true associations and intimately connected with the sinistral rotation.

In order to prove that the association with congenital heart disease is real, reliable statistics showing its incidence in the general population at different ages are required, but they are not available. Congenital heart disease causes a high mortality in the first few days of life, and the majority of those who survive this period die before they are five years old. After this age there is a steady decline in frequency owing to further deaths. The records of the Royal Victoria Montreal Maternity Hospital show a death-rate of 1.5 per cent. from this cause, and in children of ten years or less attending a children's hospital the frequency was 0.57 per cent., but as these were selected the figure is much too high. In children under 11 the frequency is probably less than 2 per cent., and still lower in each succeeding age group.

From my series I omit two cases with congenital morbus cordis, because they were published and might be regarded as selected cases. Among the remaining 55 there are five with malformation of the heart, and this number is so far in excess of that expected, assuming that in the general population the incidence is 2 per cent. or less, that I think the gene which determines complete transposition of the viscera carries with it a liability to cardiac malformation. This becomes still more probable if the age of those in my series is taken into consideration. Of the 55, three were under one year, four between one and five years, five between six and ten, eight between eleven and fifteen, and the remainder, with the exception of a small boy of unspecified age, were still older. Two of those with congenital heart disease were under one year, one was nine, and the other two were adult. Thus, of the 13 at the age most likely to show the malformation, three did so, though on my estimate not three in 100 of this age group would be expected to do so.

Recently Kartagener (1933) has called attention to the frequency with which the syndrome, hypertrophic rhinitis, nasal polyposis, sinusitis, and bronchiectasis occurs in association with complete transposition of the

viscera. Nineteen such cases have been reported, most of them within the last few years. Kartagener and his colleagues have calculated the incidence of bronchiectasis in the general population, in those with situs inversus, and of situs inversus alone, and find that they occur in association far more frequently than can be accounted for by chance. If these workers are correct, the gene must carry with it a liability to bronchiectasis. It is interesting that in my series there is a sibship of three brothers and two sisters, of which one brother has bronchiectasis and transposition of the viscera and a sister has the latter alone. Kartagener's explanation of the association is that in transposition of the viscera there is often a weakness of the bronchi, possibly due to deficiency of elastic tissue, which renders those with it liable to develop bronchiectasis.

Malformations of the heart usually lead to death before puberty, and bronchiectasis often develops in childhood and causes death before adult life is reached. If, as I believe, these two conditions are really commoner in people with situs inversus, the gene which determines it carries with it a greater liability to early death than its dominant allelomorph for normal rotation. This should gradually reduce the frequency of transposition of the viscera and ultimately lead to its extinction, if it did not arise anew from time to time by mutation of the normal gene.

*The relationship of complete to partial transposition of the viscera.* In addition to complete transposition of the viscera there are three forms of partial transposition:

- (1) Partial transposition involving both thoracic and abdominal organs.
- (2) Partial or complete transposition of the abdominal, without transposition of the thoracic viscera.
- (3) Dextrocardia, with the chambers of the heart forming a mirror image of the normal. This is most readily recognized by the inversion of the waves in Lead I of an electrocardiogram.

The relationship of these three forms to complete transposition and to one another is unknown. It seems probable that they are inherited and that they are allelomorphs, alternative genes, forming a series in a definite order of dominance, or that they are all determined by the same gene. Doolittle (1907) records a male with dextrocardia, but with the liver not transposed. His twin sister was normal. He had twin children, a boy with the viscera transposed and a normal girl. Matsueda (1929) has published the pedigree of a Japanese family in which a father and two sons had partial transposition, but the text is not available. Maekawa (1927) himself examined two sisters, one with complete transposition and the other with dextrocardia. If this were a true mirror-image dextrocardia, it is strong evidence in favour of the genetic identity of these two forms. Complete proof can be obtained only by finding other fraternities in which different forms of partial transposition or partial and complete transposition occur together. Another method of deciding whether they are allelomorphs or are determined by the same gene would be to see whether the first-cousin marriage-

rate is the same in all, or whether it varies in the different forms of partial transposition and is higher in all of them than in complete transposition. Since partial transposition of all kinds is much rarer than the complete form, the rate should be correspondingly higher in them if they are allelomorphs, and the same as in complete transposition if the gene is the same.

Dr. Stevenson has given me notes of a male Jew with mirror-image dextrocardia, transposition of the lungs, and a medially placed liver and caecum, and informed me that his parents were half-cousins. Dr. O'Reilly has told me about a boy, who was operated on for congenital pyloric stenosis and was found to have the abdominal organs all transposed, but the thoracic organs normal. His parents were not blood relations. I have seen a baby girl, a patient of Dr. Schlesinger, with gross cardiac defect causing cyanosis and with mirror-image dextrocardia, but with no transposition of the abdominal viscera. Her parents were not blood relations. A similar case is recorded by Roesler (1930), but in this instance the parents were first cousins. Though the two cousin marriages in these four cases may be significant, pointing to recessive inheritance, no conclusion can be drawn from such meagre material.

Whatever the form of partial transposition may be, the liability to defective development is far greater than in complete transposition. Mirror-image dextrocardia with partial situs inversus is, according to Abbott (1936), almost invariably associated with grave cardiac anomalies which place it in the cyanotic group, and the same applies to isolated dextrocardia of the mirror-image type, and in the latter there may be three lobes to each lung, or some other pulmonary anomaly, showing that all the thoracic organs may be involved. Risel (1909), in 49 cases of partial transposition, found that 18 had some malformation (cardiac in 15, intestinal atresia in two), and it is perhaps significant that there appears to be the same preponderance of cardiac defects as in complete transposition, though their frequency is far greater. Even in cases in which the abdominal viscera are transposed, but the heart is in the normal position and without transposition of its chambers, it is often imperfectly developed and sometimes the great vessels are transposed. In this form all kinds of malformation of the abdominal viscera are found, and here again the commonest are those also found in complete transposition, such as absence or subdivision of the spleen, and abnormalities of the genito-urinary organs and mesenteries. Even in those cases in which both thoracic and abdominal organs participate in the sinistral rotation, the lungs are often abnormal, having no lobes on one side, three lobes on both sides, or a multilobular condition, anomalies which also occur, though much less commonly, in complete transposition. In this form, too, the same malformations are found in the abdominal organs as in complete transposition, but they are very much commoner.

In each form of partial transposition there is great variability, and there seems to be an almost perfect gradation from the least to the most complete form of partial transposition, and the latter may approach very closely to

complete transposition, the only difference being the median position of the liver or the normal position of the colon.

These facts afford support for the view that all are determined by the same gene, and that the less complete the sinistral rotation, the greater the liability to malformations of the viscera. As in *Limnaea*, there may be modifying genes which interfere with complete rotation and normal development. If this is so, there can be no doubt that the gene is to some extent lethal, and, though it may not be harmful in any way to some of those homozygous for it, it may lead to the early death of others.

I hope that this paper may help to make medical men see how valuable it would be if they would systematically record and report abnormalities of this kind. For if this were done, the required data about many rare defects would soon become available for genetical study. I also hope it will be the means of bringing me more information about situs inversus.

### *Summary*

1. The thoracic and abdominal organs are at first median and symmetrical. Transposition of the viscera consists in the formation of a sinistral instead of a dextral spiral.

2. Complete transposition of the viscera is inherited as a recessive and is determined by a single autosomal gene. Proofs of this are its familial incidence and general distribution within a family, its occurrence in both members of a pair of monozygotic twins, and the high percentage of first-cousin marriages that give rise to it (six in 52 consecutive fraternities). The ratio of affected to normal sibs in the fraternities, so far as this can be ascertained, agrees with that expected of a recessive character.

3. An exceptional case of monozygotic twins, one normal and the other with transposed viscera, has been recorded. Either somatic mutation or the loss of an autosomal chromosome would account for this.

4. Most authors state that there is a great excess of males with the condition, but in my series the excess of males is small.

5. The incidence of congenital morbus cordis is abnormally high in complete transposition of the viscera, and, according to Kartagener, bronchiectasis is commoner than in normal people.

6. There are three forms of partial transposition of the viscera: that affecting both thoracic and abdominal organs, that affecting only the thoracic organs, and that affecting only the abdominal organs. Their relationship to one another and to complete transposition is discussed. Ways by which the genetic identity of the three different forms of partial transposition with one another and with complete transposition could be proved or disproved are given. For the following reasons it is suggested that all are determined by the same gene rather than by a series of allelomorphic genes. The three forms of partial transposition are not sharply separated and there is an almost perfect gradation leading up to complete transposition. Congenital

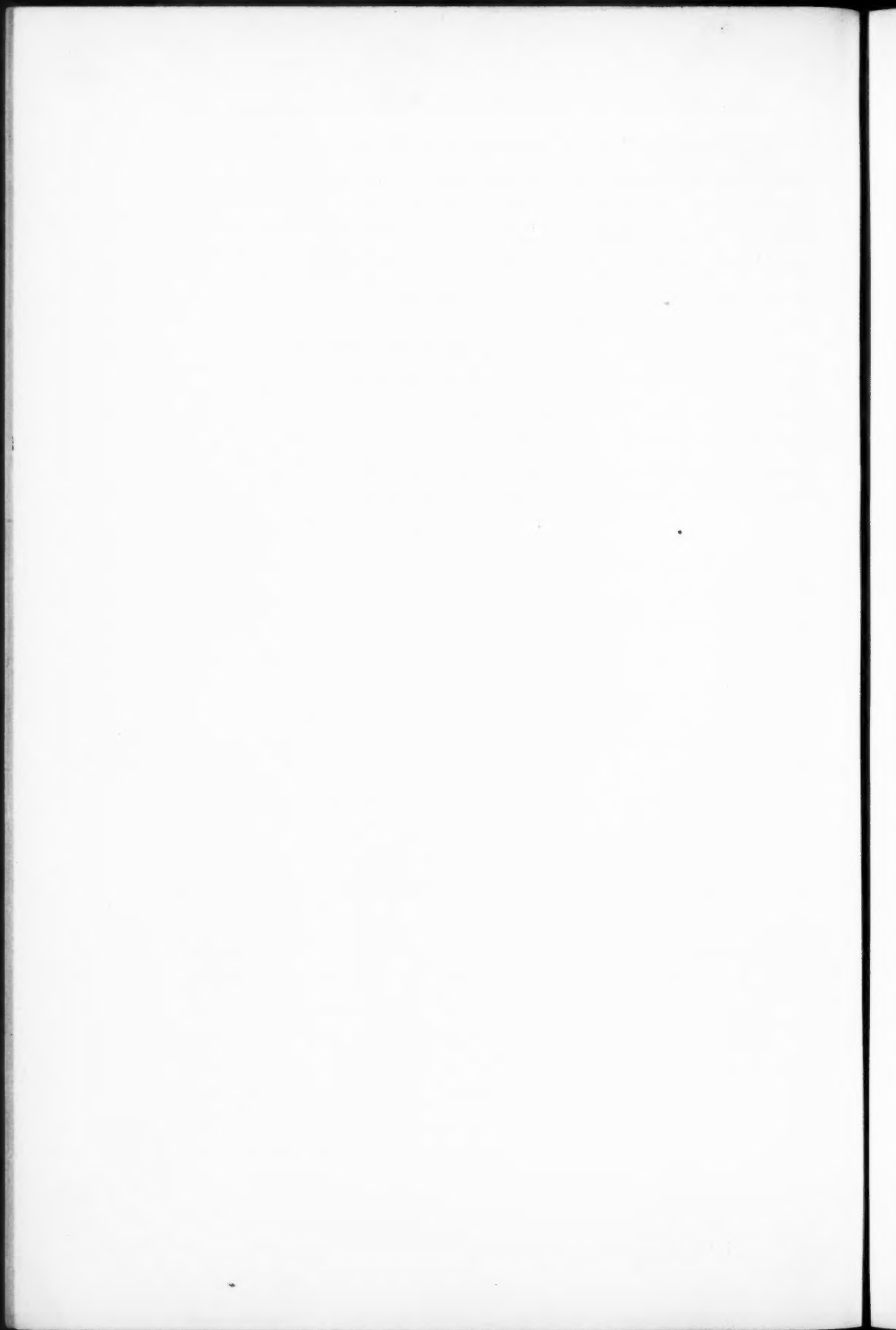
morbus cordis is much commoner in partial than in complete transposition, and the same anomalies of development of the thoracic and abdominal organs that occur occasionally in the complete form, are much commoner in the incomplete forms. Developmental anomalies are more likely to occur with sinistral than with dextral rotation of the viscera, even when sinistral rotation is complete, but they are much commoner when it is incomplete. Since many of the anomalies shorten life the gene is partially lethal.

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# THE GENETICS OF TRANSPOSITION OF THE VISCERA 493

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# ANAEMIA IN MYXOEDEMA: AND THE ROLE OF THE THYROID GLAND IN ERYTHROPOIESIS<sup>1</sup>

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## CONTENTS

### PART I. ANAEMIA IN MYXOEDEMA:

History and Summary of Previous Publications Dealing with Anaemia in Hypothyroidism . . . . .	496
Methods . . . . .	497
Case Histories . . . . .	498
Haematological Observations:	
Group I. Simple Hyperchromic Type . . . . .	502
Group II. Hypochromic Type . . . . .	511
Group III. Addisonian Hyperchromic Type . . . . .	515
Summary of the Characteristics of the Types of Anaemia Found in Association with Myxoedema . . . . .	518
Discussion of the Nature of the Varieties of Anaemia Found in Association with Myxoedema . . . . .	519

### PART II. THE ROLE OF THE THYROID GLAND IN ERYTHROPOIESIS:

Introduction . . . . .	520
Review of Observations on the Bone-marrow . . . . .	524
Summary of Clinical and Experimental Observations . . . . .	526
Note on the Use of Thyroid in the Treatment of Anaemias . . . . .	528
Discussion . . . . .	529
Summary . . . . .	532

DESPITE all that has been written on this subject, there is still need for study of the varieties of anaemia which may be found in persons with myxoedema. Moreover, the role of the thyroid in physiological erythropoiesis and the nature of the disturbances which produce anaemia are questions which have been the subject of more speculation than inquiry. The first part of this paper records the results of observations made on 10 patients with myxoedema and anaemia. The second part reviews the theories that have been put forward to explain the role of the thyroid in erythropoiesis, and develops the hypothesis that the thyroid plays no direct part in erythropoiesis, that anaemia in myxoedema, unless complicated by iron or liver deficiency, is a physiological adaptation on the part of the erythron to a diminished need of the tissues for oxygen, and that such effects of the thyroid on erythropoiesis as have been observed are indirect results of changes in the rate of metabolism.

<sup>1</sup> Received April 15, 1938.

## PART I. ANAEMIA IN MYXOEDEMA

*History and Summary of Previous Publications dealing with Anaemia in Hypothyroidism*

There is no mention of anaemia in the description of sporadic cretinism by Curling (1850), or in the description of myxoedema by Gull (1873). Charcot, writing in 1881, says: 'Tous les sujets atteints de myxoedème sont profondément cachectiques, ils sont anémiés à un haut degré. . .'. Kocher in 1883 described post-operative myxoedema, and gave the results of red-cell counts in 17 cases at varying times after total thyroidectomy. He noticed that the anaemia came on slowly over a period of months. In 1888, the report of a committee of the Clinical Society of London recorded of spontaneous myxoedema that, 'No characteristic changes are known to exist in the blood, although it must be observed that in a few cases the coloured corpuscles or the haemoglobin are diminished.' Kraepelin (1892) found the diameter of the red corpuscles increased in four cases of myxoedema, and regarded it as probable that some enlargement of the red blood-cells must be counted among the typical signs of myxoedema. He also noticed an increase in the specific gravity and in the solid constituents of the plasma. Vaquez (1897) drew diameter distribution curves of the red cells of two cretins showing the increased diameter and its diminution in the course of thyroid therapy. He noticed the sudden decrease in the number of red cells at the beginning of this treatment and the gradual increase which follows; and he concluded that the increased diameter of the red cells does not depend on the increased concentration of the plasma.

The results of subsequent investigations are made clearer by the adoption of a classification of the different types of anaemia which may be found. Bomford (1936) pointed out that the anaemias found with myxoedema could be divided into three types, which will be referred to as: (1) Simple hyperchromic anaemia; (2) Hypochromic anaemia; (3) Addisonian hyperchromic anaemia.

(1) *Simple hyperchromic anaemia.* In reports of anaemia in spontaneous myxoedema, numerous authors have included cases with a colour index slightly above 1.0 and with haemoglobin rarely, if ever, below 60 per cent. (Emery, 1923; MacKenzie, 1926; Stone, 1929; Ryle, 1930; Boros and Czoniczer, 1935; Holbøll, 1936; Sharpe, 1937). A similar type of anaemia has been reported in post-operative hypothyroidism (McCullagh and Dunlap, 1932; Stern and Altschule, 1936) and in cretinism (Wälchli, 1922; Franklin, 1934; Parsons, 1938). Macrocytosis has sometimes been reported (Kraepelin, 1892; Vaquez, 1897; Földes, 1924<sup>2</sup>; Boros and Czoniczer, 1935;

<sup>2</sup> Földes (1924) showed that the mean corpuscular volume is diminished in many cases of hyperthyroidism and increased in hypothyroidism. His results are shown in the following table:

	Under 85 cubic $\mu$ .	85 to 94 cubic $\mu$ .	Over 94 cubic $\mu$ .
Hyperthyroidism (19 cases)	52.5 %	26.5 %	21.0 %
Normal (36 cases)	8.0 %	72 %	20 %
Hypothyroidism (7 cases)	0.0 %	0.0 %	100 %

Stern and Altschule, 1936), but this type is quite distinct from Addisonian anaemia and does not respond to treatment with liver extract (Baldrige and Greene, 1934; Holbøll, 1936; Sharpe, 1937). Several authors have commented on the absence of excessive anisocytosis, of poikilocytosis, or of signs of regeneration in stained films (Wälchli, 1922; Emery, 1923; Franklin, 1934; Stern and Altschule, 1936). Others have shown that this type improves slowly on prolonged treatment with thyroid alone (MacKenzie, 1926; Stone, 1929; Boros and Czoniczer, 1935), but records of a return to completely normal figures on this treatment alone have only recently been published (Franklin, 1934; Sharpe, 1937). No record, with an adequate control period, has been found of the occurrence of a reticulocyte response on treatment with thyroid.

(2) *Hypochromic anaemia.* Cases of anaemia with a lower colour index have been included in the series of most of the authors quoted above. They have also been reported by Minot (1921), Warfield and Green (1925), and Baker (1925). Ryle (1930) reported a case in which the haemoglobin was 25 per cent. and the patient had a smooth glazed tongue and an enlarged spleen, in addition to the signs of myxoedema. The administration of iron and thyroid is necessary to secure a complete remission in this type (Lerman and Means, 1932; Sharp, 1937). Holbøll (1936) treated simple hyperchromic and hypochromic cases with both iron and thyroid, and claimed that there is no difference in the response to therapy of the two types. There are no satisfactory studies of the kind of reticulocyte response which may occur on treatment with iron and thyroid.

(3) *Addisonian hyperchromic anaemia.* A small number of cases of this type have been recorded (Means, Lerman, and Castle, 1931; Boros and Czoniczer, 1935; Holbøll, 1935). The anaemia may be of any degree of severity, and the colour index is usually higher than in uncomplicated Addisonian anaemia. It fails to respond to treatment with thyroid alone, but responds rapidly to combined treatment with thyroid and a liver or stomach preparation.

#### *Methods*

The observations reported here were made on 10 patients with myxoedema. Eight of them were observed as in-patients, and daily reticulocyte counts, with capillary blood counts on every third or fourth day, were made for periods of from one to three months. All the haematological investigations were made by the same observer (R. R. B.).

Blood for capillary counts was taken from the lobe of the ear and was diluted in a haemocytometer pipette with a 0.1 per cent. solution of gentian violet in normal saline. Red- and white-cell counts were made on the same sample in a Bürker chamber. The percentage of haemoglobin was estimated by Haldane's standard, whereby 100 per cent. of haemoglobin is equivalent to 18.5 per cent. oxygen capacity (13.8 gm. of haemoglobin per 100 c.c.). For reticulocyte counts, equal parts of blood and of a cresyl blue solution (consisting of one part of saturated alcoholic solution of brilliant cresyl blue

to five parts of a 1 per cent. solution of sodium citrate in normal saline) were mixed on a paraffined slide and incubated in a moist chamber at 37° C. for fifteen minutes; smears of this mixture were made in the usual manner and counterstained with Jenner's stain. The number of reticulocytes in 1,000 red cells was then counted. The mean corpuscular diameter of 500 red cells (M.C.D.) was determined by the method of Price-Jones (1933). The methods and calculations described by Price-Jones, Vaughan, and Goddard (1935) were used in the determination of the mean corpuscular volume (M.C.V.), the mean corpuscular haemoglobin (M.C.H.), and the mean corpuscular haemoglobin concentration (M.C.H.C.). The fragility of the red cells in varying strengths of saline was estimated and represented graphically by a modification of the method devised by Creed (Vaughan, 1937). An observation on a normal person was made as a control with each fresh stock of saline.

Gastric function was estimated by the usual gruel fractional test meal, specimens being withdrawn at intervals of fifteen minutes for three hours. Histamine hydrochloride 0.5 mg. was injected at the end of the first one and half hours.

Thyroid was given in the form of Thyroideum B.P. by mouth in the doses indicated in the figures. Iron was given as Pil. Ferri Carb. (Blaud's pill) in gelatin capsules in doses of 30 gr. three times a day.

#### *Case Histories*

*Case 1.* L.H. Female, aged 53. London Hospital Reg. No. 41147/35. Came to hospital complaining of lassitude.

*History.* For two years, feeling unwell, unusually sensitive to cold, voice becoming hoarse. For eighteen months, pains and sensation of numbness in feet, feeling tired. For six weeks, voice increasingly hoarse, actions becoming slow, skin dry.

*Previous history.* Twenty years before admission, bilateral tubo-oophorectomy for 'a tumour'—no more information available. Three years before admission, spent four weeks in a hospital following an apparently hysterical collapse.

*Physical examination.* Pale. Skin dry and rough. Fine dry hair. Hoarse voice. Some puffiness of face and lower eyelids. Blood-pressure 120/85. No abnormality detected in chest, heart, or nervous system.

*Special investigations.* Fractional test meal, slight hyperchlorhydria before and normal response after injection of histamine. Basal metabolic rate, 75 per cent. of normal. Blood-cholesterol, 0.23 gm. per 100 c.c. Stools, no occult blood detected. Van den Bergh reaction, direct negative, indirect 0.6 mg. per 100 c.c. of serum.

*Case 2.* E.B. Female, aged 49. London Hospital Reg. No. 41733/35. Came to hospital for dental treatment.

*History.* For ten years, lassitude, some dyspnoea on exertion, unusually sensitive to cold. For one year, hair falling out. For six months, voice becoming 'croaky', becoming slow and drowsy. For three months, puffiness under the eyes.

*Previous history.* Artificial menopause induced with radium at St. Bartholomew's Hospital ten years previously.

*Physical examination.* Temperature usually 97°. Pulse about 65. Almost bald. Eyebrows very scanty. Dry thickened skin. Cream-coloured com-

plexion. Severe pyorrhoea. Great puffiness below the eyes. Blood-pressure 160/110. Chest, abdomen, and nervous system, no abnormality detected.

*Special investigations.* Fractional test meal, complete achlorhydria before and after injection of histamine. Basal metabolic rate, 62 per cent. of normal. Blood-cholesterol, 0.4 gm. per 100 c.c. Stools, no occult blood detected.

*Case 3.* A.C. Female, aged 60. London Hospital Reg. No. 23190/35. Admitted with a head injury, having been knocked down by a lorry.

*Physical examination.* Temperature usually 97°. Pulse about 65. Fat. Some pallor. Dull myxoedematous expression. Dry thick skin. Blood-pressure 110/70. Chest, numerous râles. No abnormality detected in abdomen or cardiovascular system.

*Special investigations.* Fractional test meal, achlorhydria before, normal response after injection of histamine. Basal metabolic rate, 74 per cent. of normal. Blood-cholesterol, 0.27 gm. per 100 c.c. Stools, no occult blood detected.

*Case 4.* M.S. Female, aged 53. London Hospital Reg. No. 40065/36. Came to hospital complaining of weakness in the back.

*History.* For three years, hair falling out, becoming slower at her work, increasing constipation. For three months, voice 'croaking', weakness of back.

*Previous history.* No illnesses.

*Physical examination.* Temperature 98°. Pulse about 100. Moderately deaf. 'Strawberry and cream' complexion. Almost bald. Dry thick skin. Large supraclavicular pads. Slow laborious speech. Considerable dorsal kyphosis. Blood-pressure 150/80. Protuberant abdomen. No abnormality found in chest or nervous system.

*Special investigations.* Fractional test meal, normal acidity before and normal response after injection of histamine. Basal metabolic rate, 74 per cent. of normal. Blood-cholesterol, 0.27 gm. per 100 c.c. Stools, no occult blood detected.

*Case 5.* H.M. Female, aged 67. London Hospital Reg. No. 41764/35. Came to hospital complaining of weakness.

*History.* For one year, following car accident, loss of energy, bifrontal headaches, slowness of movements, becoming increasingly susceptible to cold, some failure of memory, voice becoming husky.

*Previous history.* Menopause twenty-three years previously. In 1929, abscess of scalp.

*Physical examination.* Temperature usually 97°. Pulse about 80. Slow in speech and movement. 'Strawberry and cream' complexion. Dry coarse skin. Scanty eyebrows. Hair dry and sparse. Blood pressure 165/105. No abnormality discovered in chest, abdomen, or nervous system.

*Special investigations.* Fractional test meal, complete achlorhydria before and after injection of histamine. Basal metabolic rate, 74 per cent. of normal. Blood-cholesterol, 0.33 gm. per 100 c.c.

*Case 6.* A.P. Female, aged 34. London Hospital Reg. No. 41125/35. Came to hospital complaining of loss of energy.

*History.* For three years, told by doctor that she was anaemic, treated with pills and improved. For two years, loss of energy, forgetfulness and deterioration of intelligence, dyspnoea on exertion, skin and hair becoming dry and coarse, unusually sensitive to cold. For seven months, moderately severe menorrhagia.

*Previous history.* Nothing relevant.

*Physical examination.* Temperature 98°. Pulse about 70. Lethargic. Puffy face. Coarse hair. Dry coarse skin. Small supraclavicular pads. Monotonous voice. Blood-pressure 120/90. No abnormality found in the chest, abdomen, or nervous system.

*Mental condition.* On admission, very slow mentality, at times anxious and weeping. Shortly after admission became confused, with delusions and occasional hallucinations. At times apathetic and depressed, at times agitated.

*Special investigations.* Fractional test meal, achlorhydria before, normal response after injection of histamine. Basal metabolic rate could not be determined, as patient became agitated when test was attempted.

*Case 7.* A.T. Female, aged 47. London Hospital Reg. No. 40543/36. Came to hospital complaining of weakness.

*History.* Two years previously, investigated as possible case of pernicious anaemia. Since then, easily tired, depressed, dyspnoeic on exertion, paraesthesiae in hands. For one year, unusually susceptible to cold. For six months, skin rough, hair greying, some failure of memory, catamenia regular with no excessive loss.

*Previous history.* Nothing relevant.

*Physical examination.* Temperature 97°. Pulse about 65. Lethargic. Slow speech and husky voice. Pallor of mucous membranes. Cream-coloured complexion. Puffiness of face, hands, and feet. Scanty eyebrows. Sub-miliary yellow deposits on eyelids. Patchy yellowness of skin of palms and soles. Blood-pressure 120/85. No abnormality found in the chest, abdomen, or nervous system.

*Special investigations.* Fractional test meal, normal acidity before, and normal response after injection of histamine. Basal metabolic rate, 66 per cent. of normal. Blood-cholesterol, 0.44 gm. per 100 c.c.

*Case 8.* E.S. Female, aged 55. London Hospital Reg. No. 41244/36. Came to hospital complaining of weakness.

*History.* For five years, lacking in energy, hair falling out. For one year, feeling of weakness in legs and back, susceptible to cold, dyspnoeic on exertion.

*Previous history.* Menopause one year previously.

*Physical examination.* Temperature usually 97°. Pulse about 75. Obese, with small supraclavicular pads. Puffiness under the eyes. Dry coarse skin. Hair dry and scanty. Blood-pressure 210/110. No abnormality found in the chest, abdomen, or nervous system.

*Special investigations.* Fractional test meal, complete achlorhydria before and after injection of histamine. Basal metabolic rate, 78 per cent. of normal. Stools, occult blood test negative.

*Case 9.* B.G. Female, aged 46. London Hospital Reg. No. 41687/36. Came to hospital complaining of lack of energy and soreness of tongue.

*History.* Eight years before this admission was an in-patient in the London Hospital for the investigation of abdominal pain. Found to have a moderate hypochromic anaemia. Red blood-cells 4.7 millions, haemoglobin 55 per cent., colour index 0.59, white blood-cells 8,360. Five years before admission, attended as an out-patient, myxoedema diagnosed, treated with thyroid. Attended erratically for three years. For twenty months (without treatment), lacking energy, unusually susceptible to cold, swelling of hands and feet, tongue sore.

*Previous history.* In 1914, gland of neck removed. In 1918, admitted

four times to a sanatorium, definite evidence of tuberculosis never found. Menopause one year before admission. No history of menorrhagia.

*Physical examination.* Temperature often 97°. Pulse about 75. Apathetic. Scanty eyebrows. Considerable pallor. 'Strawberry and cream' complexion. Dry harsh skin, with generalized puffiness of subcutaneous tissues. Large tongue with transverse fissuring and some general atrophy of papillae, and a central band where papillae were completely absent. Rhagades at angles of mouth. Longitudinal ridging of brittle nails, some showing slight koilonychia. Blood-pressure 120/70. No evidence of arteriosclerosis. Soft mitral systolic murmur. No abnormality found in the chest, abdomen, or nervous system.

*Special investigations.* Fractional test meal, complete achlorhydria before and after injection of histamine. Barium meal, no evidence of organic disease. Basal metabolic rate, 82 per cent. of normal. Blood-cholesterol, 0.23 gm. per 100 c.c. Stools, no occult blood detected.

*Case 10.* C.H. Female, aged 49. London Hospital Reg. No. 41235/36. Admitted to hospital complaining of weakness.

*History.* Ten years before admission, suddenly fainted and fell, was in bed for a month and has never felt quite well since. For eight years, feeling unsteady, loss of sensation in hands; numbness, coldness, heaviness, and 'pins and needles' in legs. Six years before admission, following another fainting attack was unable to walk for six months, gradually regained use of her legs and was able to walk with help. For four years, painful swelling of interphalangeal joints, 'pins and needles' in hands, headaches, feeling of coldness in legs. For ten months, hair falling out, eyesight deteriorating, speech becoming more difficult, shortness of breath, palpitation. For five weeks, considerable improvement following treatment with hog's stomach preparation.

*Previous history.* At 14 years of age, had fainting attacks, said to have been anaemic, menstruation began at 17. At 21 years of age, treated for twelve weeks for a goitre in hospital. At 26 years of age, in hospital with asthma and bronchitis, goitre still present. At 29 years of age, had 'double pneumonia'.

*Previous treatment.* Had been treated with liver, and probably with thyroid, at times, for eight years. Six years before admission was said to have pernicious anaemia, treated with liver extract, but not regularly.

*Family history.* Five sisters and two brothers alive and well. Three siblings died in infancy. Two children alive and well, two miscarriages.

*Physical examination.* Thin. Skin slightly yellow. Cyanosis of brightly coloured nose and cheeks. Skin dry and coarse, with patchy brown pigmentation of neck, face, and forearms. Hair of head and eyebrows scanty. Little pubic or axillary hair. Slight enlargement of right lobe of thyroid. No atrophy of mucous membrane of tongue. Blood-pressure 150/100. No evidence of cardiac enlargement. Chest, crepitations at left base. Abdomen, spleen not felt. Nervous system, intelligence normal, speech slurred, concomitant strabismus, slight weakness of lower right facial muscles, other cranial nerves normal, slight analgesia over peripheral part of upper limbs, abdominal reflexes absent, lower limbs showed normal nutrition, power, tone, and co-ordination, vibration sense absent at ankles, knee-jerks sluggish, ankle-jerks absent, plantar responses extensor.

*Special investigations.* Fractional test meal, complete achlorhydria before and after injection of histamine. Basal metabolic rate, 77 per cent. of normal. Wassermann reaction, negative. Blood-cholesterol, 0.4 gm. per 100 c.c. Van den Bergh reaction, direct negative, indirect 0.7 mg. per

100 c.c. of serum. Stools, occult blood test negative. Plasma protein, 6.8 gm. per cent. Alkali reserve, 64.8 volumes per cent. of carbon dioxide. Electrocardiogram, normal rhythm, left ventricular preponderance, low voltage curve, T-wave flat in all leads. Orthodiagram, heart full size, aorta uncoiled, some narrowing of trachea in region of thyroid.

TABLE I

*Blood Counts in Ten Cases of Myxoedema.*

Case.		B.M.R. per cent.	R.B.C. in millions.	Haemo- globin (Haldane) per cent.	Colour index.	M.C.D. in $\mu$ .	Macro- cytosis per cent.
<i>Simple Hyperchromic Type.</i>							
1. L. H.	Female, 53	75	3.4	78	1.15	8.35	48.4
2. E. B.	Female, 49	62	3.6	76	1.06	7.92	17.4
3. A. C.	Female, 60	74	2.6	60	1.15	7.93	16.2
4. M. S.	Female, 53	74	4.0	81	1.01	7.88	14.4
<i>Hypochromic Type.</i>							
5. H. M.	Female, 67	74	3.6	66	0.92	7.96	19.5
6. A. P.	Female, 34	—*	3.8	62	0.82	8.19	36.4
7. A. T.	Female, 47	66	3.8	48	0.63	7.12	0.0
8. E. S.	Female, 55	78	4.4	78	0.89	7.56	0.4
9. B. G.	Female, 46	82	4.2	46	0.55	7.45	1.4
<i>Addisonian Hyperchromic Type.</i> (After treatment with liver factor.)							
10. C. H.	Female, 49	77	3.8	82	1.08	8.56	48.4

\* Mental state made determination impossible.

*Haematological Observations*

Of the 10 cases, four were of the simple hyperchromic type; five were of the hypochromic type; and one was of the Addisonian hyperchromic type.

*Group I. Simple Hyperchromic Type (Cases 1 to 4)*

The blood findings in the four cases before treatment are shown in Table I. In each case the anaemia was hyperchromic and macrocytic. A red-cell count of 2.6 millions and a haemoglobin of 60 per cent. were the lowest figures recorded. In stained films, the appearance of the red cells was characteristic; they were well stained and macrocytosis was present, but there was no poikilocytosis and no abnormal degree of anisocytosis. In the films of the cases with a raised reticulocyte count before treatment, there were a few polychromatophilic cells and occasional cells with fine basophil punctation. No primitive cells were seen.

*Response to treatment.* The blood counts before treatment, the first normal figures recorded, and the duration of treatment before these figures were reached are shown in Table II. Cases 1, 2, and 3 were treated with thyroid alone, and Case 4 was treated with iron and thyroid together. The rate of response to treatment was very slow, the average time before the red cells and haemoglobin reached normal values being five and three-quarter months.

The course of the response of Case 1 to treatment with thyroid alone is shown in detail in Fig. 1. The anaemia remained constantly hyperchromic in type throughout a control period of twenty-four days without treatment; there were considerable fluctuations in the red-cell count and haemoglobin percentage during this time. When thyroid was given, the red-cell count

TABLE II

*Response to Treatment in Four Cases of Simple Hyperchromic Anaemia in Myxoedema Treated with Thyroid.*

Case.	Before Treatment.			After Treatment with Thyroid.			Length of Treatment in Months.
	R.B.C. in millions.	Haemoglobin (Haldane) per cent.	Colour index.	R.B.C. in millions.	Haemoglobin (Haldane) per cent.	Colour index.	
1. L. H.	3.4	78	1.15	4.9	99	1.01	3½
2. E. B.	3.6	76	1.06	5.2	100	0.96	9
3. A. C.	2.6	60	1.15	5.5	94	0.85	3½
*4. M. S.	4.0	81	1.01	4.9	94	0.95	7½

\* Treated with thyroid and iron.

rose faster than the percentage of haemoglobin, so that the anaemia became hypochromic in type about one month after the beginning of treatment. Normal values for red cells and haemoglobin were not recorded till treatment had been continued for approximately three and a half months.

The course of the response to treatment was similar in all four cases; in two of them (Cases 2 and 4) the rate of response was much slower than in the others. These two patients had clinically the severest myxoedema, though they had not the severest anaemia.

The observations of Baldridge and Greene (1934), Holbøll (1936), and Sharpe (1937) show that liver therapy has no effect on this type of anaemia. Since it is macrocytic in type and the mean corpuscular haemoglobin concentration is normal in every case, it is unlikely to be affected by iron therapy. Before this investigation was begun, Case 1 had been treated with iron for various periods with no effect on her anaemia. Case 7 developed this type of anaemia while she was under treatment with iron alone for five months (Fig 10). Case 4 was treated with iron and thyroid simultaneously, but the red cells and haemoglobin did not become normal for seven months, so that the additional iron therapy did not hasten the course of the response (Fig. 3).

The simple hyperchromic type of anaemia disappears slowly on prolonged treatment with thyroid alone. The slowness of the response is a curious feature, which will be discussed later. Iron and liver therapy have no effect on the course of the response.

*Reticulocytes.* The reticulocyte count in Case 1 fluctuated during the control period without treatment between 0.7 per cent. and 5.2 per cent. (Fig. 1). Known causes of a raised reticulocyte count were excluded. In the course of treatment the reticulocyte count fell towards normal, but was

still above normal at the end of eleven weeks. A reticulocyte count fluctuating between 1.0 and 3.6 per cent. during a control period of sixteen days was also seen in Case 2. Case 3 was first seen on the day after an accident,

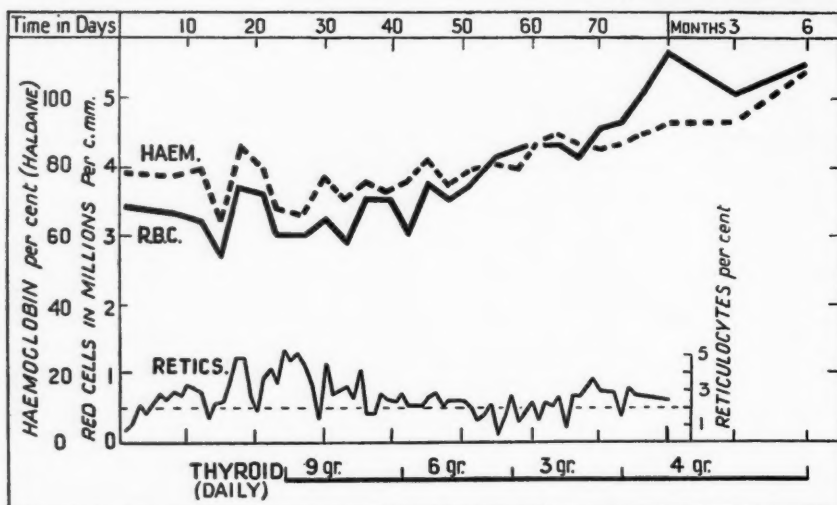


FIG. 1. Showing course of the response to treatment with thyroid of a case of anaemia of the simple hyperchromic type in myxoedema (Case 1, L. H.).

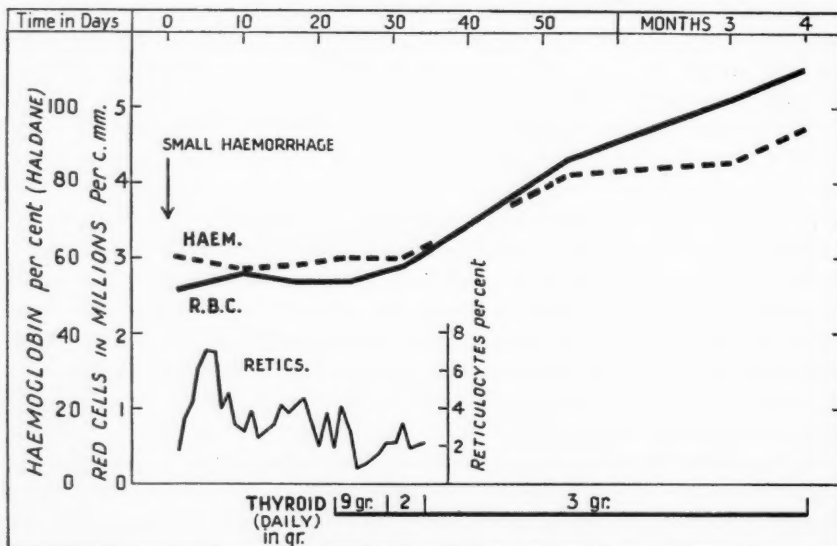


FIG. 2. Showing a reticulocyte response following a haemorrhage, and the course of the response to treatment with thyroid in a case of anaemia of the simple hyperchromic type in myxoedema (Case 3, A. C.).

as a result of which she had bled from a scalp wound. There occurred (Fig. 2) what appears to be a qualitatively normal reticulocyte response,

rising to 3.5 per cent. on the second day after the haemorrhage and 7.1 per on the fifth day. The reticulocyte count in Case 4 was within normal limits

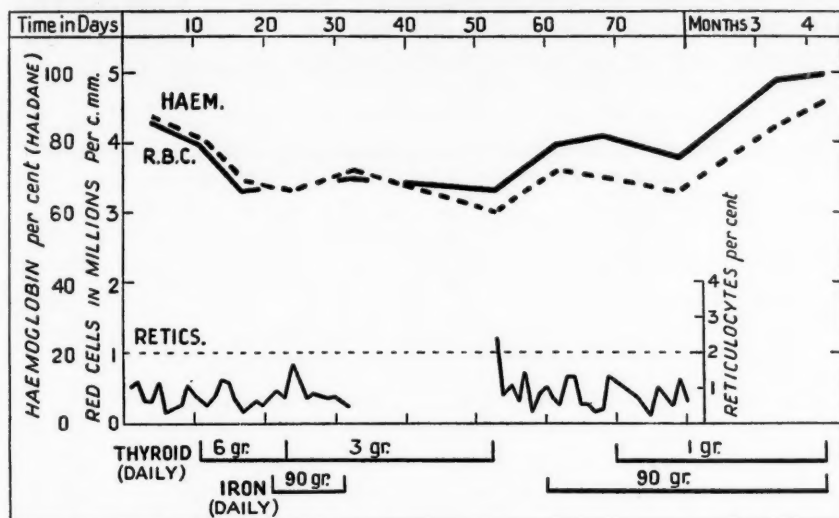


FIG. 3. Showing the absence of reticulocyte responses on treatment of a case of anaemia of the simple hyperchromic type in myxoedema with thyroid and with iron (Case 4, M. S.).

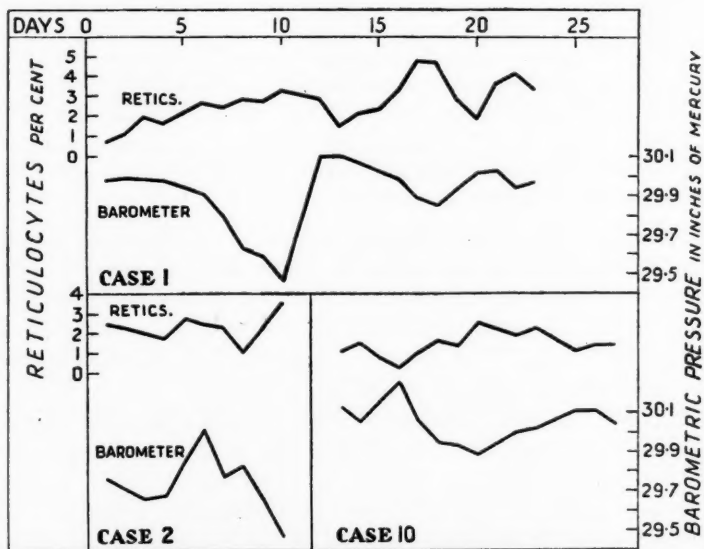


FIG. 4. Curves showing the percentage of reticulocytes in three untreated cases of anaemia in myxoedema with simultaneous barometric readings.

during a control period of ten days (Fig. 3). No reticulocyte response was observed at the beginning of treatment with thyroid, nor during ten-day

periods of treatment with iron in the second and third weeks, and again in the eighth and ninth weeks, when the anaemia had become hypochromic in type. Small, but recognizable, reticulocyte responses on treatment with thyroid and with iron occurred in cases initially of the hypochromic type with similar red-cell and haemoglobin values before treatment (Fig. 8).

TABLE III

*Red-cell Characteristics in Four Cases of Simple Hyperchromic Anaemia in Myxoedema Before and After Treatment with Thyroid.*

	M.C.D. in $\mu$ .	$\sigma$ .	v. per cent.	Macro- cytosis.	M.C.V. in cu. $\mu$ .	M.C.H. in $\gamma\gamma$ .	M.C.H.C. per cent.
Normal limits	6.69 to 7.72*		5.33 to 7.32*		75.7 to 96.1†	24.0 to 29.8†	28.2 to 34.4†
Case 1. L. H.							
Before	8.35	0.57	6.85	48.4	103.2	34.7	33.6
After	7.41	0.50	6.67	0.0	88.9	29.1	32.7
Case 2. E. B.							
Before	7.92	0.53	6.64	17.4	91.7	28.3	30.9
After	7.28	0.48	6.53	0.0	80.0	25.2	31.5
Case 3. A. C.†							
Before	7.93	0.62	7.88	16.2	101.9	29.2	28.6
After	7.73	0.44	5.71	3.0	85.4	24.4	28.6
Case 4. M. S.							
Before	7.88	0.52	6.56	14.4	94.7	29.3	31.0
After	7.45	0.48	6.48	0.0	80.5	22.9	28.4

Abbreviations. M.C.D. = mean corpuscular diameter.  
 $\sigma$  = standard deviation.  
 v. = coefficient of variation.  
 M.C.V. = mean corpuscular volume.  
 M.C.H. = mean corpuscular haemoglobin.  
 M.C.H.C. = mean corpuscular haemoglobin concentration.

\* Price-Jones (1933).

† Price-Jones, Vaughan, and Goddard (1935).

‡ Suffered from well-marked emphysema, and had had an acute haemorrhage two weeks before the first series of observations.

In an attempt to find some explanation for the fluctuations which were observed in Cases 1 and 2, the figures for the reticulocyte count were plotted against the barometric pressure, as recorded at Greenwich Observatory, about two miles from the London Hospital (Fig. 4). Comparison of the two curves suggests that there may be an inverse relationship of some kind between the reticulocyte percentage and the barometric pressure.

Case 10, who had been adequately treated with a stomach preparation before she came to hospital, presented as a case of the simple hyperchromic type, and was the only other case of the series with a raised reticulocyte count before treatment. In this case the reticulocyte count was plotted against the barometric pressures recorded at the hospital at the same time as the reticulocyte count was made. The inverse relationship between the two curves (Fig. 4) appeared to be closer than in the first two cases.

*Changes in size and haemoglobin content of the red cells.* These are summarized in Table III. In each case a small degree of macrocytosis (average 24.1 per

cent. of macrocytes) was present before treatment, but the red-cell diameter distribution curves were normal in shape ( $\sigma$  and  $v$ . within normal limits)<sup>3</sup>, a finding which is in keeping with the absence of excessive anisocytosis in the stained films. This finding distinguishes the macrocytosis in these cases from that found in liver deficiency anaemias. In the course of treatment

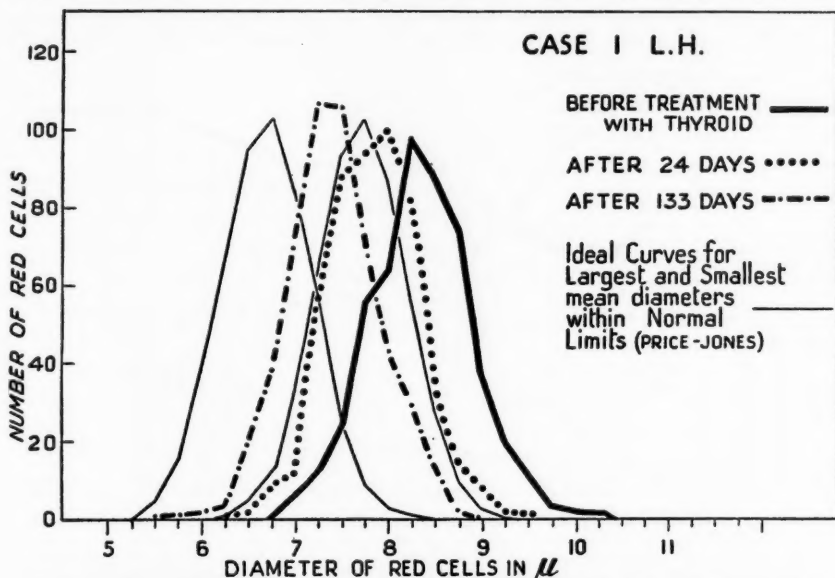


FIG. 5. Changes in the red-cell diameter distribution curve in a case of anaemia of the simple hyperchromic type in myxoedema during treatment with thyroid (Case 1, L. H.).

with thyroid, the mean corpuscular diameters and mean corpuscular volumes slowly became normal. Red-cell diameter distribution curves before and during treatment illustrating this change in Case 1 are shown in Fig. 5. The reduction in mean corpuscular volume was accompanied by a proportional reduction in mean corpuscular haemoglobin, so that the mean corpuscular haemoglobin concentration remained constant.

These various changes during treatment in Case 2 are shown in more detail in Fig. 6. The changes observed occur in two periods, a short one of one or two weeks, followed by a longer one of months. During the first two weeks of treatment there occurred a rapid increase to normal in the basal metabolic rate and a corresponding decrease in the blood-cholesterol. At the same time there was a sudden fall in the red-cell count (first noticed by Vaquez in 1897) and in the volume of packed cells in the haematocrit tube, accompanied by a temporary *increase* in the already raised mean corpuscular volume. These three changes in the blood can be accounted for by known changes in the blood-volume and concentration. The blood-volume is reduced

<sup>3</sup> Except in Case 3, where there had been an acute haemorrhage two weeks before the curve was drawn.

in myxoedema, and may be increased by 25 per cent. or more by treatment with thyroid (Thompson, 1925; Rowntree and Brown, 1929; Chang, 1931), the increase in blood-volume occurring at the same time as the increase in the basal metabolic rate. This increase in the blood-volume accounts for the decrease in the red-cell count, which is seen in the majority of cases at the

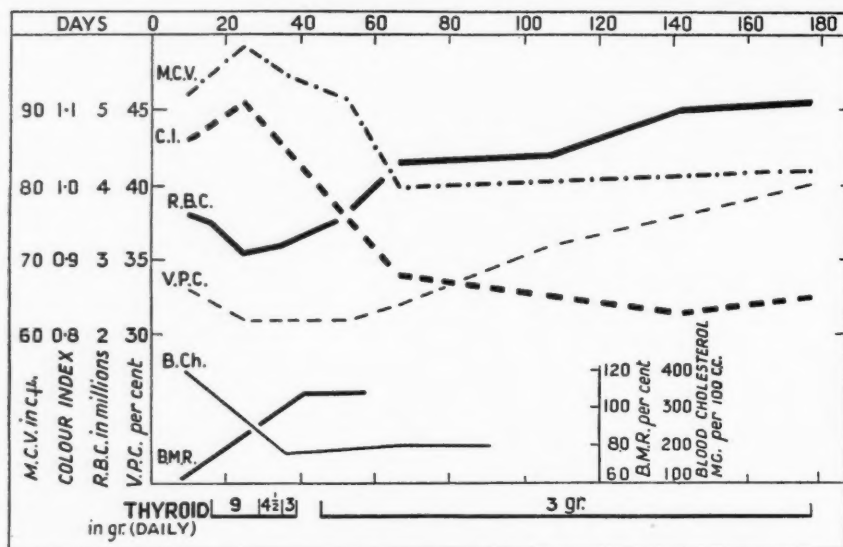


FIG. 6. Changes in the number of red cells (R.B.C.), the colour index (C.I.), the volume of packed cells (V.P.C.), the mean corpuscular volume (M.C.V.), the basal metabolic rate (B.M.R.), and the blood-cholesterol (B.Ch.) in a case of anaemia of the simple hyperchromic type in myxoedema during treatment with thyroid (Case 2, E. B.).

beginning of treatment. The increase in the blood-volume is accompanied by a decrease in the proteins, refractive index, and viscosity of the plasma (Kendall, 1929; Decourt, Meyer, and Guillaumin, 1935). A reduction in the osmotic tension of the plasma occurs at the same time, and accounts for the temporary increase in the size of the red cells. The increased concentration of the plasma before treatment would be expected to produce a diminution in the size of the red cells. It therefore provides no explanation of the macrocytosis present before treatment, nor of the gradual decrease of cell size to normal, which follows the temporary increase at the beginning of treatment. During the second period of treatment, lasting some months, the red-cell count increases slowly to normal, and the red-cell size decreases to normal. The increase in the percentage of haemoglobin follows that of the red cells, so that the colour index decreases until the red-cell count reaches normal and then increases again. The mean corpuscular haemoglobin concentration remains constant.

*Changes in the fragility of the red cells.* Curves representing the percentage of red cells haemolysed in different strengths of saline are shown in Fig. 7 (a). These show that the fragility of the red cells in this type of anaemia is

slightly but constantly increased, haemolysis beginning in concentrations of saline of 0.54, 0.52, and 0.48 per cent. respectively (normal 0.42 to 0.46 per cent.). The curve of Case 3 approached the 'increased-span type', to be described later as characteristic of the hypochromic type of anaemia, a discrepancy which may be associated with the fact that this was the patient

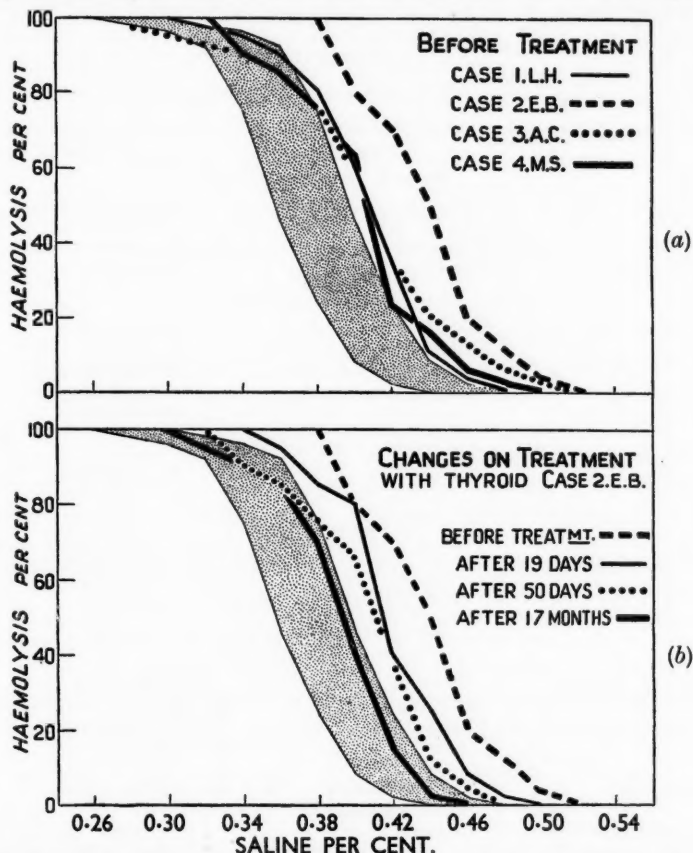


FIG. 7. Curves showing the fragility of the red cells in four cases of anaemia of the simple hyperchromic type in myxoedema before treatment and the changes in one case during treatment with thyroid.

who had recently suffered from a haemorrhage. In the course of treatment with thyroid the fragility returned slowly to normal. The changes on treatment in Case 2 are illustrated in Fig. 7 (b).

**Gastric function.** The results of test meals before treatment are shown in Table IV. Two of the four cases had physiological test-meal results, and only one showed achlorhydria after injection of histamine.

**Differential diagnosis from Addisonian anaemia.** In a considerable proportion of the cases of simple hyperchromic anaemia in myxoedema reported in the literature, a diagnosis of pernicious anaemia had been made before the

myxoedema was recognized. In both conditions there may be a yellowish pallor, no loss of weight, paraesthesiae, difficulty in walking, achlorhydria, and a high colour-index anaemia with leucopenia, so that confusion may well arise if the distinctive clinical features of myxoedema are not prominent. In difficult cases it should be possible to reach a correct diagnosis if attention is given to the points of distinction summarized in Table V.

TABLE IV

*Gastric Function in Ten Cases of Myxoedema and Anaemia.*

Case.	Before Injection of Histamine.	After Injection of Histamine.
<i>Simple Hyperchromic Type.</i>		
1. L. H.	Slight hyperchlorhydria	Normal response
2. E. B.	Achlorhydria	Achlorhydria
3. A. C.	Achlorhydria	Normal response
4. M. S.	Normal	Normal response
<i>Hypochromic Type.</i>		
5. H. M.	Achlorhydria	Achlorhydria
6. A. P.	Achlorhydria	Normal response
7. A. T.	Normal	Normal response
8. E. S.	Achlorhydria	Achlorhydria
9. B. G.	Achlorhydria	Achlorhydria
<i>Addisonian Hyperchromic Type.</i>		
10. C. H.	Achlorhydria	Achlorhydria

TABLE V

*Differential Diagnosis between Simple Hyperchromic Anaemia in Myxoedema and Pernicious Anaemia.*

	Simple Hyperchromic Anaemia in Myxoedema.	Pernicious Anaemia.
Severity of anaemia	Never severe	Often severe
Appearance of red cells	Macrocytosis without excessive anisocytosis. No poikilocytosis. ( $\sigma$ and v. normal)	Megalocytosis. Anisocytosis. Poikilocytosis. ( $\sigma$ and v. increased)
Gastric acidity	May be normal. May be achlorhydria	Achlorhydria
Basal metabolic rate	Reduced	Increased (Baldrige and Barer, 1931)
Blood-cholesterol	Increased	Reduced (Gorham and Myers, 1917)
Yellowness of complexion	Due to carotinaemia. Serum bilirubin normal	Due to hyperbilirubinaemia. Serum bilirubin increased
Effect of treatment	No response to liver. Slow response to thyroid	Rapid response to liver. No response to thyroid

*Note on carotinaemia in myxoedema.*<sup>4</sup> Stannus (1929) reported the case of a patient with myxoedema and xanthosis cutis. Escamilla, Lisser, and Shepardson (1935) reported the case of a woman of 45 years with myxoedema and slight carotinaemia. Wendt (1935) found the serum carotin normal in

<sup>4</sup> The term 'carotinaemia' has been used for convenience in place of 'hyperlipochromaemia', since carotin is the principal, though not the only, lipochrome in human serum.

one case of myxoedema, but increased in two out of a series of 11 cretins. A yellowish complexion was noticed in a number of the cases reported in this paper. As the serum bilirubin was within normal limits in every case it seemed likely that the colour was due to an excess of lipochromes. The serum lipochromes were estimated by the method of Boeck and Yater (1929) in the last two patients only of the series, and the results were expressed as the lipochrome index, the normal limits, calculated from the figures of White (1931), being 0.3 to 1.4. Both patients were taking a normal diet. In Case 7 there was slight localized xanthosis of the palms and soles, as well as a diffuse yellowish tinge of the skin and sclerotics. The lipochrome index on four occasions, during a period of five months before treatment with thyroid was begun, was 4.0, 4.3, 3.5, and 3.2. After one month of treatment with thyroid, and again in the seventh month, it was 1.0. In Case 10, before treatment with thyroid, it was 6.0, and after ten days of treatment it was 2.3. In two cases not included in this series, in which the yellow colour was not so noticeable, it was 2.5 and 1.6 before treatment.

Slight jaundice can be distinguished from a yellow colour due to carotinaemia by a simple qualitative test. Equal quantities of serum, absolute alcohol, and petroleum ether are mixed in a centrifuge tube, shaken, and centrifuged for two or three minutes. The mixture separates into three distinct layers, and the yellow colour is seen in the middle or alcohol layer if it is due to jaundice, and in the upper or petroleum ether layer if it is due to carotinaemia. It is desirable that a larger number of cases should be investigated from this point of view. But from the evidence available a provisional conclusion may be drawn, that the yellowish complexion of patients with myxoedema is due to carotinaemia. This is associated, as it is in diabetes, with a raised blood cholesterol (Hurxthal, 1934; Lesné, Briskas, and Lardé, 1935). As the colour of cream is due to the presence of lipochromes, the use of the term 'strawberry and cream' complexion to describe the colouring of the myxoedematous facies is not without justification.

#### *Group II. Hypochromic Type (Cases 5 to 9)*

The blood findings in five cases before treatment are shown in Table I. In two cases macrocytosis was present, whereas in three it was insignificant or absent. A number of poorly stained red cells and varying degrees of poikilocytosis and anisocytosis were present in the films of all cases. When there was no macrocytosis, the appearance of the stained film closely resembled that of idiopathic iron deficiency anaemia, though definite microcytosis was never seen. No primitive cells were seen. The red-cell diameter distribution curves were either normal in form or showed moderate irregularity and widening of the base, as is found in idiopathic iron deficiency anaemia. The mean corpuscular diameter and the mean corpuscular volume diminished on treatment with thyroid in every case in which they were measured.

*Response to treatment.* All cases in this group were eventually treated

with both iron and thyroid. Two were treated for varying periods with thyroid alone, and three with iron alone.

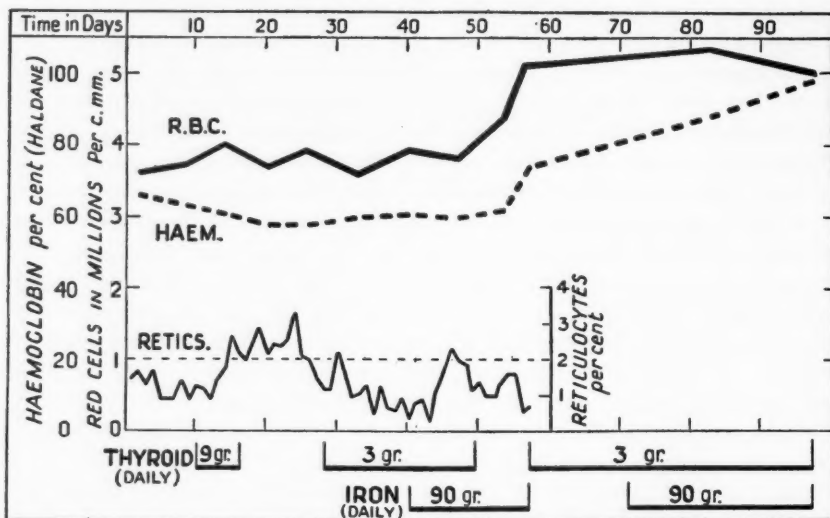


FIG. 8. Showing reticulocyte responses to treatment with iron and with thyroid in a case of anaemia of the hypochromic type in myxoedema (Case 5, H. M.).

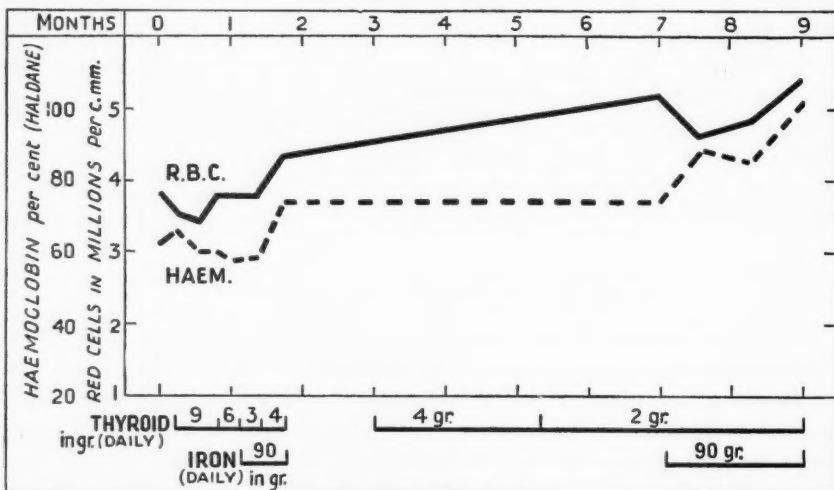


FIG. 9. Showing the effect of treatment with thyroid and iron respectively in a case of anaemia of the hypochromic type in myxoedema (Case 6, A. P.).

Case 5 was treated with thyroid alone for one month, and subsequently with iron and thyroid together. The results of treatment are shown in Fig. 8. In the course of treatment for one month with thyroid alone, the number of red cells remained almost constant and the percentage of haemo-

globin fell slightly. On further treatment for ten weeks with iron and thyroid together, the blood count rose rapidly to normal.

Case 6 (Fig. 9) was treated with thyroid alone for one month with the same result. She was then treated with iron and thyroid together for sixteen days, during which period the red blood-cells rose from 3.7 to 4.6 millions

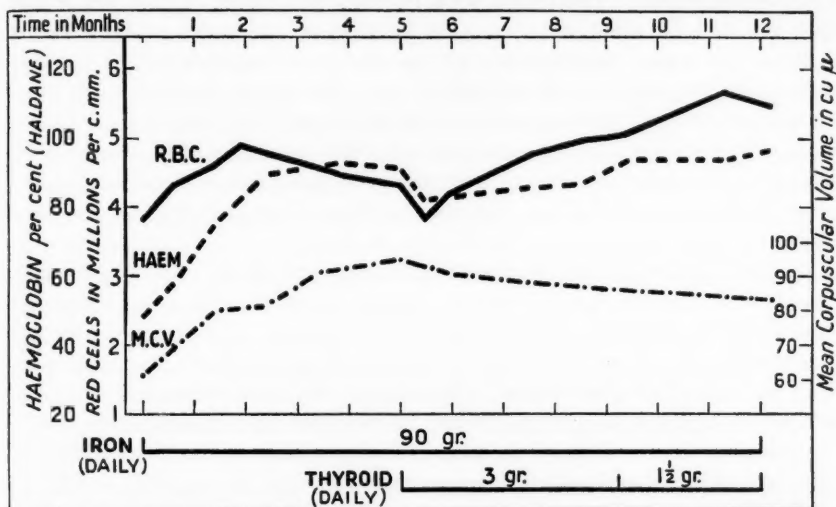


FIG. 10. Showing the effect of treatment with iron alone and with iron and thyroid in a case of anaemia of the hypochromic type in myxoedema (Case 7, A. T.).

per c.mm. and the haemoglobin from 57 to 74 per cent. Treatment with iron was then discontinued and treatment with thyroid alone was continued for a further five and a half months, during which period the red-cell count rose to 5.2 millions per c.mm., but the haemoglobin remained stationary at 74 per cent. When iron therapy was begun again, the haemoglobin percentage promptly rose, and at the end of two months of the combined treatment the red-cell count was 5.9 millions per c.mm. and the haemoglobin was 102 per cent. In these two cases there was a satisfactory response to combined treatment with iron and thyroid, but no increase of haemoglobin on treatment with thyroid alone.

Case 7 was treated for five months with iron alone (Fig. 10). The red-cell count rose rapidly and reached 5.0 millions per c.mm. at the end of the second month; it then fell slowly and was 4.3 millions at the end of the fifth month, when treatment with thyroid was begun. The percentage of haemoglobin rose from 49 to 93 in the fourth month and was 91 at the end of the fifth month. The mean corpuscular volume rose steadily from 61 cubic  $\mu$  to 95 cubic  $\mu$  at the end of the fifth month, and the blood picture became hyperchromic in type in the fourth month. As the patient had a moderately severe myxoedema it was thought inadvisable to withhold thyroid for a further period. At the end of five months of treatment with iron, the blood picture had become hyperchromic and slightly macrocytic in type, the

blood count was falling, and it was apparent that the patient had developed a mild degree of anaemia of the simple hyperchromic type previously described. This interpretation of the observations is borne out by two other findings, first by the change in the type of the red-cell fragility curve, to be described later, and secondly by the course of the subsequent response to thyroid treatment. Treatment with thyroid was begun at the end of the fifth month and the blood count fell in the first two weeks to red cells 3.9 millions per c.mm., haemoglobin 82 per cent., and colour-index 1.05. The subsequent response closely resembled that of a simple hyperchromic case. In spite of the combined administration of iron and thyroid, normal figures were not recorded till seven months after the beginning of treatment with thyroid. The bearing of these observations on the question of the mechanism concerned in the production of the two types of anaemia will be discussed later.

Case 8 was also treated for five months with iron alone. The blood count rose in the same way in the first two months from red cells 4.4 millions per c.mm. and haemoglobin 78 per cent. to red cells 4.9 millions per c.mm. and haemoglobin 94 per cent. In the remaining three months of treatment with iron the count fell slowly again. Treatment with thyroid was begun at the end of the fifth month, but in this case treatment with iron was discontinued at the same time. After seven months further treatment with thyroid alone the red-cell count was 4.6 millions per c.mm. and the haemoglobin had fallen to 74 per cent.

Case 9 had been under observation with a hypochromic anaemia (haemoglobin varying between 34 per cent. and 55 per cent.) for seven years before this investigation was begun, and had been treated at various times with both iron and thyroid. Her haemoglobin in the last three years had never been higher than 51 per cent. She was treated for one month with iron alone, during which time her red-cell count fell from 4.2 to 3.7 millions per c.mm., and her haemoglobin rose from 46 to 52 per cent. Thereafter she was treated with iron and thyroid for sixteen months. The red-cell count at first rose steadily and reached 5.1 millions per c.mm. five months after the beginning of the combined treatment. It has remained between 4.0 and 5.0 millions. The haemoglobin rose slowly to 68 per cent. nine weeks after the beginning of the combined treatment, and 84 per cent. ten months after the beginning of the combined treatment. The response to treatment in this case differed from that in the other four, in all of whom there was a prompt and considerable rise in the percentage of haemoglobin on treatment with iron and thyroid, or with iron alone. This very slow response may have been due to the length of time for which the anaemia had been present, and to the fact that there were present such other signs of iron deficiency anaemia as brittle nails and a severe degree of atrophy of the mucous membrane of the tongue. Trials of treatment with marmite and liver extract were without effect.

The observations made on these five cases show that for practical purposes

combined treatment with iron and thyroid is necessary in cases of this type and that the response is usually rapid and satisfactory. Theoretically it is of interest that in no case of this type was any increase in the percentage of haemoglobin observed on treatment with thyroid alone; in two cases there was a rapid but temporary response to treatment with iron alone; and in one of them, as treatment with iron alone was continued, the temporary response was followed by the slow development of an anaemia of the simple hyperchromic type.

*Reticulocytes.* The reticulocytes were observed during a control period and during treatment in three of the five cases of this type. In each case small but recognizable responses followed the administration of both iron and thyroid. These are illustrated in Case 5 (Fig. 8). Similar responses to 3.6 per cent. on the eighth day of treatment with thyroid and 3.4 per cent. on the third day of treatment with iron were observed in Case 6. There were similar but more prolonged and irregular responses, rising to 3.5 per cent. on the third day of treatment with iron, and 2.6 per cent. on the tenth day of treatment with thyroid in Case 9. The responses to treatment with iron were small, but of the usual type; the responses to treatment with thyroid reached their peaks on the eighth, tenth, and fourteenth days of treatment respectively. The reticulocyte count during the control period remained normal in every case.

*Changes in the fragility of the red cells.* Curves representing the percentage of red cells haemolysed in different strengths of saline in four of the five cases of this type are shown in Fig. 11 (a). In three of them the curves are of the 'increased span' type which is found in cases of idiopathic iron deficiency anaemia (Daland and Worthley, 1934). In the fourth, the least hypochromic of the four, with a colour index of 0.89, the curve shows a slightly increased fragility and resembles that seen in the simple hyperchromic type. Fig. 11 (b) shows the changes in Case 7 on treatment with iron and thyroid. At the beginning of treatment the patient's curve was of the 'increased span' type. After five months of treatment with iron, when the blood picture had become hyperchromic and slightly macrocytic, the red-cell fragility curve was of the type seen in the simple hyperchromic cases, and after a further seven months of treatment with iron and thyroid the curve was within the limits of normal.

*Gastric function.* The results of fractional test meals before treatment are shown in Table IV. In one case the test-meal result was physiological and in three of the five cases there was achlorhydria before and after the injection of histamine.

### *Group III. Addisonian Hyperchromic Type. (Case 10)*

Observations were made on one case of this type (Case 10). Before the patient came to hospital she had been treated with a hog's stomach preparation as a case of pernicious anaemia. Considerable subjective improvement

had followed this treatment, but as no blood counts had been done the diagnosis of pernicious anaemia had not been proved.

When the patient was seen in hospital a diagnosis of myxoedema was made and the blood count was typical of the simple hyperchromic type of anaemia in myxoedema: red cells 3·8 millions per c.mm., haemoglobin

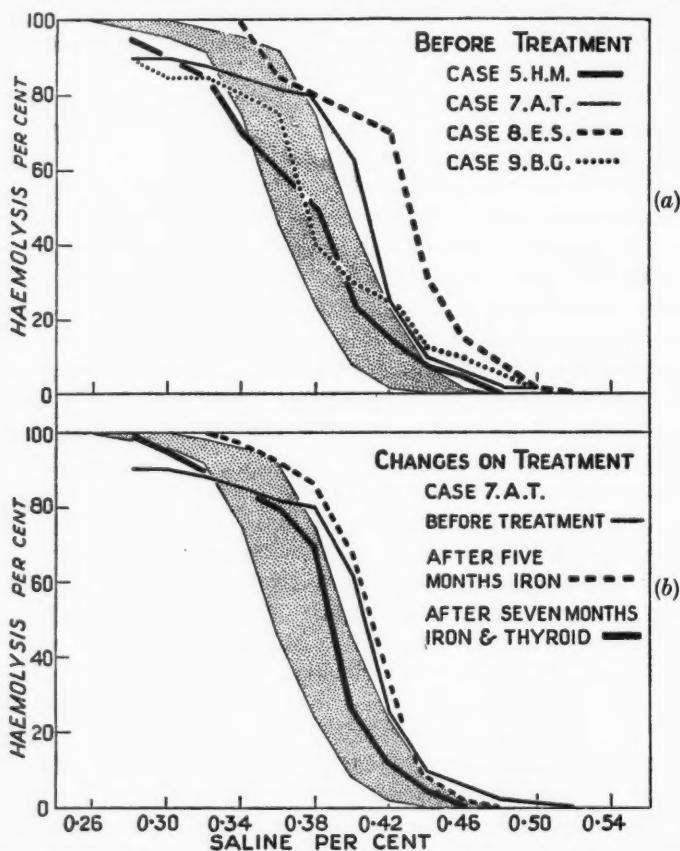


FIG. 11. Curves showing the fragility of the red cells in four cases of anaemia of the hypochromic type in myxoedema and the changes in one case during treatment with thyroid.

82 per cent. (Haldane), colour index 1·08, reticulocytes 1·3 per cent., white cells 2,700, polymorphonuclears 46 per cent., lymphocytes 42 per cent., eosinophils 3 per cent., basophils 1 per cent., large mononuclears 8 per cent. The stained film showed red cells normal in shape and staining, and larger than normal in size; mean corpuscular volume 100 cubic  $\mu$ , mean corpuscular haemoglobin 28·6  $\gamma\gamma$ , mean corpuscular haemoglobin concentration 28·6 per cent. The serum bilirubin was 0·7 mg. per 100 c.c. and the lipochrome index of the serum was 6·0 (normal 0·3 to 1·4), so that the yellowness of the complexion noticed clinically was due to carotinaemia and not to jaundice.

The fractional test meal showed achlorhydria before and after the injection of histamine.

At this time there were no unequivocal signs of subacute combined degeneration of the cord, as the plantar responses were indefinite. It was therefore uncertain whether this was a case of myxoedema with the simple hyper-

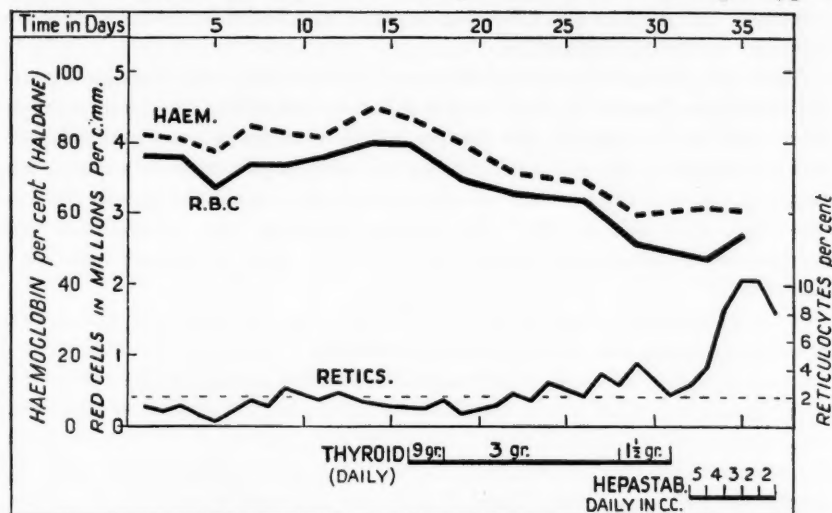


FIG. 12. Showing the effect of treatment with thyroid and the reticulocyte response on treatment with hepastab in a case of anaemia of the Addisonian hyperchromic type in myxoedema. This patient had been treated with hog's stomach before coming to hospital, and on admission her blood picture was that of a case of the simple hyperchromic type (Case 10, C. H.).

chromic type of anaemia, which had been treated mistakenly as pernicious anaemia, or whether it was a case of myxoedema and the Addisonian hyperchromic type of anaemia, in which the liver deficiency had been treated and the picture of the simple hyperchromic type of anaemia in myxoedema had resulted. Subsequent observations showed that the latter was the correct explanation.

The patient was given no treatment for sixteen days, during which time the blood count altered very little (Fig. 12). The reticulocytes fluctuated, and on one occasion rose to 2.6 per cent. She was then treated for fifteen days with thyroid, and her blood count fell steadily to red cells 2.6 millions per c.mm., haemoglobin 60 per cent., and colour index 1.12. The red cells increased in size (to mean corpuscular volume of 112 cubic  $\mu$ ). Definite megalocytosis, together with anisocytosis, occasional poikilocytosis, polychromatophilia, and occasional punctate basophilia, appeared in the blood films. At the end of this period the serum bilirubin was 0.3 mg. per 100 c.c. and the lipochrome index had fallen to 2.3. On the thirty-second day, treatment with thyroid was discontinued and daily intramuscular injections of hepastab were begun. The reticulocytes rose steadily and reached a peak of 10.3 per cent. on the fourth day of this treatment. There was at the same time a notable

improvement in the clinical condition, but the plantar responses became indubitably extensor in type. On the sixth day of treatment with hepastab the patient became suddenly extremely ill. Her complexion was greyish and her pulse could not be counted. An electrocardiogram showed auricular flutter with a one-to-one rhythm and a rate of approximately 225 beats per minute. She died on the following day and was found *post mortem* to have a recent myocardial infarction.

This case presented as a typical one of myxoedema with a simple hyperchromic type of anaemia. But in view of the history of improvement on treatment with hog's stomach, the relapse which occurred when this treatment was discontinued, the qualitatively typical reticulocyte response when it was begun again, and the presence of signs of subacute combined degeneration of the cord, it is evident that the correct diagnosis was myxoedema and Addisonian hyperchromic anaemia in remission after treatment with hog's stomach.

It is unfortunate that there is no blood count available for the period before the patient was originally treated with hog's stomach. The observation that after this treatment she presented as a case of the simple hyperchromic type of anaemia is, however, particularly interesting in that it is analogous to the observation made in Case 7, in which an anaemia of the hypochromic type was similarly changed into one of the simple hyperchromic type by treatment with iron alone.

*Summary of the Characteristics of the Types of Anaemia found in Association with Myxoedema*

1. *The simple hyperchromic type.* This type is never severe. The colour index is normal or a little above 1.0. There is some macrocytosis, but no poikilocytosis and no excessive anisocytosis. The reticulocyte count may be normal or a little above normal. The serum bilirubin is normal, and when the skin is yellow, the colour is due to carotinaemia. The fragility of the red cells in saline is slightly increased. The gastric function may be normal or there may be achlorhydria. The anaemia disappears very slowly on prolonged treatment with thyroid alone. There is no reticulocyte response. The administration of liver or of iron has no effect on the anaemia.

2. *The hypochromic type.* This type may be of any severity, and an enlarged spleen, a glazed tongue, and nail changes may be present. Except in the matter of cell size, the blood picture closely resembles that of idiopathic iron-deficiency anaemia. There may or may not be macrocytosis, but microcytosis was absent in the cases reported here. Some degree of poikilocytosis and some excess of anisocytosis is present. The reticulocyte count is normal. The fragility of the red cells in saline is of the 'increased span' type. There may or may not be complete gastric achlorhydria. The anaemia usually responds rapidly to combined treatment with iron and

thyroid. There are small but recognizable reticulocyte responses at the beginning of treatment with iron or with thyroid.

3. *The Addisonian hyperchromic type.* This type may be of any severity. Other signs of pernicious anaemia such as a glazed tongue may be present, as may evidence of subacute degeneration of the cord. The blood picture closely resembles that of uncomplicated pernicious anaemia, but the colour index is often higher than in the uncomplicated anaemia. There is definite megalocytosis, with poikilocytosis, excessive anisocytosis, and polychromatophilia. The serum bilirubin is usually raised. Complete gastric achlorhydria is present. The anaemia responds rapidly to combined treatment with thyroid and a liver preparation.

*Discussion of the Nature of the Varieties of Anaemia found in Association with Myxoedema*

The anaemia here referred to as the simple hyperchromic type is considered to be the uncomplicated anaemia of myxoedema for the following reasons:

(1) It is the only type which is completely repaired by treatment with thyroid alone.

(2) It is the type of anaemia which appeared in the large majority of a series of patients with hypothyroidism following total thyroidectomy for the relief of congestive heart failure or angina pectoris (Stern and Altschule, 1936).

(3) It exactly resembles that observed in young rabbits after thyroidectomy (Kunde, Green, and Burns, 1932).

(4) The observations recorded here, so far as they go, suggest that cases of the hypochromic and Addisonian types can be converted into the simple hyperchromic type by treatment respectively with iron alone or with a liver preparation alone.

There is nothing in the haematological findings to suggest that the hypochromic and the Addisonian hyperchromic types of anaemia found in association with myxoedema are anything more than alimentary iron and liver deficiency anaemias modified by the co-existence of myxoedema. If it is the case that these anaemias occur more frequently in myxoedematous than in non-myxoedematous persons of the same age and sex, it is probable either that hypothyroidism may lead to gastric or intestinal dysfunction, or that anaemia may predispose a patient to develop hypothyroidism, or that both conditions may depend on the same unknown antecedent cause. There is experimental evidence that thyroid administration affects gastric secretion, and clinical evidence that achlorhydria is common in both hyperthyroidism and hypothyroidism (Lerman and Means, 1932; Berryhill and Williams, 1932). The familiar observation of a tendency towards constipation in myxoedema and of diarrhoea in over-dosage of thyroid also indicates that the thyroid has some effect on the intestinal tract.

## PART II. THE ROLE OF THE THYROID GLAND IN ERYTHROPOIESIS

*Introduction.* It seems to be agreed that a relationship of some kind exists between the thyroid gland and haemopoiesis. The nature of this has been the subject of investigations, but remains obscure. Harrington (1933) wisely wrote that 'anaemia is not a constant feature of myxoedema, and it is uncertain whether the thyroid has any direct effect on the haemopoietic activity of the bone-marrow or not'. The implication that the finding of normal blood figures in some cases of myxoedema might be used as an argument against the existence of any effect of the thyroid on erythropoiesis is, however, open to question, as the blood-volume has been found to be diminished by about 25 per cent. in cases in which it has been determined (Thompson, 1925; Rowntree and Brown, 1929; Holbøll, 1930; Chang, 1931).

The theories that have been held to explain this relationship and the hypothesis which it is intended to put forward in this paper may be stated as follows:

(1) Horsley (1886), whose observations first proved the endocrine function of the thyroid gland, claimed that the gland was itself an actively haemopoietic organ.

(2) Subsequently it was suggested, among other theories, that the thyroid hormone had a direct stimulating action on haemopoiesis (Perrin and Hanns, 1923); that the anaemia of hypothyroidism was due to a depression of the function of the haemopoietic system, akin to diminished function of other tissues (Stone, 1928). Zondek (1935) considers that 'haematopoiesis and the distribution of the blood within the body are regulated essentially by the thyroid hormone'.

(3) In the last decade research into the pathology of pernicious anaemia has led to the conception of dyshaemopoietic anaemias, due to deficiency of factors necessary for the normal maturation of red cells in the bone-marrow. Most authors recently have assumed that thyroxine is such a factor, that its absence from the bone-marrow causes an arrest in the maturation of red cells, and that anaemia in myxoedema should be considered a form of deficiency dyshaemopoietic anaemia (Witts, 1932; Vaughan, 1936; Castle and Minot, 1936; Whitby and Britton, 1937; Parsons, 1938). The respective parts played by maturation factors and by oxygen lack in the repair of the dyshaemopoietic deficiency anaemias has been outlined by Minot and Castle (1935). Oxygen lack remains the only known stimulus to erythropoiesis. It is acting strongly in a patient with a dyshaemopoietic anaemia, and the bone-marrow, therefore, undergoes hyperplasia. This does not lead to an increased delivery of red cells into the circulation, because of a lack of one or other of the factors necessary for the normal maturation of red cells. The administration of the appropriate factors does not stimulate erythropoiesis; it supplies the missing factor and allows the stimulus of oxygen lack to increase the supply of red cells into the circulation, until such time as the state of oxygen lack is abolished.

It is characteristic of the indisputable deficiency anaemias that they may

be of any severity, if the deficiency is maintained; that there is some hyperplasia of the red marrow, and in the blood film such signs of dyshaemopoiesis<sup>5</sup> as poikilocytosis, excessive anisocytosis, and sometimes the presence of primitive cells; and that there occurs, when the deficient factor is supplied, a characteristic reticulocyte response and a more or less rapid repair of the anaemia. I have not found a case recorded of simple hyperchromic anaemia in hypothyroidism (even after total thyroidectomy) that is of more than moderate severity; the scanty evidence available of the condition of the bone-marrow (see below) suggests that there is a relative aplasia; poikilocytosis and excess of anisocytosis are absent; primitive cells are never seen; no reticulocyte response occurs in human patients, and the repair of the anaemia by thyroid is extremely slow. It is unlikely, though it is not impossible, that an anaemia which differs in so many ways from the known deficiency dyshaemopoietic anaemias should be of the same nature. Moreover, administration of the known maturation factors does not raise the blood count in persons who have no deficiency of them. Administration of thyroid causes a temporary erythrocytosis in normal animals (Power, 1934) and in non-myxoedematous patients (Hoskins and Jellinek, 1932).

(4) Wälchli (1922) commented on the absence of what he referred to as 'signs of regeneration' in the blood films of a series of cretins, of whom the majority had an anaemia of the simple hyperchromic type. He suggested that the anaemia in these cases should be regarded not as a disease, but as an adaptation to the patients' diminished metabolism. The hypothyroid subject uses less oxygen in the tissues, and needs, therefore, less red cells and haemoglobin to carry oxygen to the tissues.

Boycott (1929) introduced the convenient term 'erythron' for the red cells and red-cell-forming tissues. Physiological hypertrophy of the erythron has only one known cause, a deficient supply of oxygen to the tissues. It occurs both in rarefied air and in exposure to gas mixtures deficient in oxygen at atmospheric pressure. That atrophy of the erythron occurs in the presence of an excess of oxygen is not so generally recognized. It was first demonstrated by Doyon and Morel (1901) in rabbits kept in a caisson in the Rhône, and later by Bornstein (1911) in dogs and an ape exposed to increased pressures in a caisson used in the building of the Elbe tunnel. Campbell (1926, 1927) made extensive observations of the effect upon rabbits and other animals of exposure for prolonged periods to various oxygen tensions at atmospheric pressure. Exposure to reduced oxygen tension for several weeks produced a slow increase in haemoglobin and red cells with a fall in the colour index (e.g. to 0.77); exposure to increased oxygen tension caused a decrease in red cells and haemoglobin, along with a rise in the colour index (e.g. to 1.22). After return to a normal oxygen tension the animals' blood took several weeks to return to normal. Some typical results are shown in Fig. 13, reprinted from Campbell's paper. He estimated the

<sup>5</sup> The term dyshaemopoiesis, as used in this article, refers only to qualitative disturbance in erythropoiesis.

oxygen tension in the tissues and found it raised when the oxygen tension in the inspired air was raised. Writing of the anaemia which occurs in these circumstances, he says: 'It is obvious from these great decreases of haemoglobin and red cells that the body strenuously opposes excess of oxygen in the tissues.'

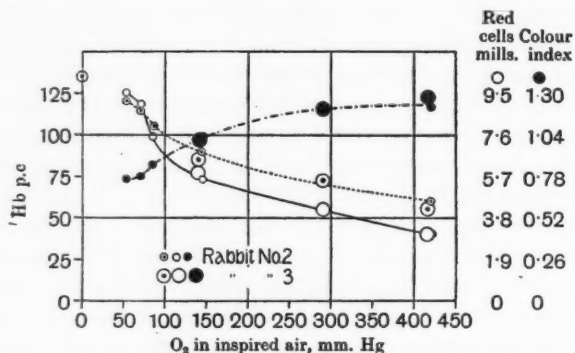


FIG. 13. Curves showing the effect on the blood of rabbits of prolonged exposures to altered pressure of oxygen in the inspired air. (From Campbell, 1926.)

If atrophy of the erythron occurs as an adaptation to an increase of oxygen supply in the inspired air, it seems likely that it might also occur with a diminished consumption of oxygen by the tissues. It might be said that either contingency presents the erythron with the same problem. It is, therefore, of interest to inquire whether the anaemia which appeared in animals exposed to increased tension of oxygen and the simple hyperchromic type of anaemia found in myxoedema are alike in their haematological characteristics.

The animals exposed to increased tension of oxygen developed a hyperchromic anaemia with colour indices up to 1.22. No changes were found in the shape or size of the red cells. Changes in the shape of red cells are obvious on inspection of a film, but changes in size in the absence of changes in shape are far from obvious. Since no measurements of the size of the cells were recorded, it was perhaps permissible to question the statement that no change in the size of the red cells occurred. Doyon and Morel (1901) measured the diameters of the red cells of their rabbits exposed to increased pressures, and recorded an increase in the red-cell diameter with the anaemia. Smith, Belt, Arnold, and Carrier (1925) recorded a polycythaemia in four men and two women who went from sea-level for a stay of four weeks at an altitude of 11,000 feet, and observed a gradual decrease in their mean corpuscular volume, measured by the haematocrit, as the polycythaemia developed.<sup>6</sup> It is perhaps, therefore, more likely that changes in the size of the red cells in Campbell's animals were overlooked, than that there occurred such an increase in the haemoglobin concentration of the red cells as would

<sup>6</sup> Cf. Földes' observations on the mean corpuscular volume in hyper- and hypothyroidism in footnote on page 496.

be necessary to permit an increase of colour index to 1.22 with no change in the size of the red cells. It is indeed doubtful whether supersaturation of red cells with haemoglobin can occur (Jorgensen and Warburg, 1927; Andresen and Mugrage, 1936). If, then, there was an increase in the size of the red cells of the animals exposed to increased oxygen tension, their anaemia resembles that of hypothyroidism very closely. Both show a raised colour index and macrocytosis, but no poikilocytosis or excessive anisocytosis, or other sign of dyshaemopoiesis.

In healthy individuals changes in oxygen consumption are usually associated with corresponding changes in cardiac output. It might therefore be expected that there would be a proportionate reduction in cardiac output, when the oxygen consumption is reduced in hypothyroidism. Such a reduction has indeed been reported by Field and Bock (Means, 1925) in two cases of myxoedema; and in a number of cases of hypothyroidism after total thyroidectomy for angina pectoris without any signs of congestive heart failure (Altschule and Volk, 1935, 1936). In these cases the reduction in cardiac output was approximately equal to that of basal metabolic rate. With a reduction of oxygen consumption of about 30 per cent. there was a reduction in cardiac output of about 40 per cent. The authors claim that this difference is significant and that at levels of basal metabolism below -15 per cent. the reduction in cardiac output is actually greater proportionately than that of basal metabolic rate. It appears, therefore, at first sight that reduction in cardiac output in hypothyroidism may compensate for reduction in oxygen consumption, and that atrophy of the erythron need not be invoked as a part of the process of compensation. This argument, however, fails to consider the significance of the amount of haemoglobin in the circulation.

A simple speculation may help to elucidate the question. If it were possible to amputate a quarter of an animal's body without otherwise damaging the animal, it might be expected that the oxygen consumption, the cardiac output, and the amount of haemoglobin in the circulation would all be reduced by approximately 25 per cent., and the factors concerned in the transport of oxygen from the atmosphere to the tissues would be in a state of equilibrium at a lower level of metabolism. The state of an animal after total thyroidectomy, as far as these factors are concerned, appears to be somewhat analogous. The oxygen consumption and cardiac output are reduced by approximately 30 per cent., but reduction in the amount of haemoglobin in the circulation appears only very slowly. If the disproportion that has been reported between the reduction in cardiac output and in basal metabolic rate is significant, it may indeed be explained by this delay in the reduction in the amount of haemoglobin in the circulation.

The haemoglobin was above 90 per cent. in all the patients in the first series reported by Altschule and Volk, and above 85 per cent. in those in the second series. Stern and Altschule (1936) have shown, however, that over a period of several months after thyroidectomy the haemoglobin may diminish

to a level of 70 per cent. There do not appear to be any observations of the cardiac output in patients whose haemoglobin has fallen to this level, but one may suggest that such observations might show a proportionate reduction in oxygen consumption, cardiac output, and haemoglobin in the circulation; in other words, that these factors would be found to have attained a new equilibrium at the lower level of metabolism.

One may therefore reasonably suggest that atrophy of the erythron is to be expected in hypothyroidism, in spite of the fact that there is a diminished cardiac output, and in spite of the claim that the reduction in cardiac output, in patients with no more than a slight degree of anaemia, is proportionately greater than the reduction in basal metabolic rate.

This hypothesis of the relationship of the thyroid to erythropoiesis may be restated briefly as follows: There is no evidence of dyshaemopoiesis in anaemia in hypothyroidism, when this is uncomplicated by gastrogenous iron or liver factor deficiencies; and, therefore, no evidence that thyroxine is utilized in the bone-marrow in erythropoiesis. It is suggested that there occurs in hypothyroidism a partial atrophy of the erythron, as an adaptation to the diminished need of the tissues for oxygen, and that this adaptation is analogous to that which occurs in animals exposed to an increased oxygen tension of the inspired air.

#### *Review of Observations on the Bone-marrow*

1. *Bone-marrow in cretinism.* Langhans (1897) examined the bone-marrow of a cretin of fourteen months. Red marrow normal for the child's age was found only in the clavicles. There is no mention of the marrow in the ribs and vertebrae. There was fatty marrow in the humerus, radius and ulna, femur, tibia and fibula. Under the microscope, fatty marrow was present almost to the line of ossification, with traces of normal marrow next to the zone of cartilage cells. Maresch (1898) described an autopsy on a girl 11 years old with a congenital defect of the thyroid gland. Macroscopically the thyroid gland was absent. The long bones were short and plump, with no abnormal softness or curvature, and the marrow cavities were smaller than normal. The marrow was fatty in type throughout the long bones, and failed to show an amount of cellular (which he refers to as 'lymphatic') marrow corresponding to the age of the patient. Dieterle (1906) described the marrow in the case of a female cretin 50 cm. long, the age is not stated. Macroscopically the marrow of the limb bones was rich in fat. The marrow spaces appeared deserted, and there were few free red cells and erythroblasts. In the vertebrae and sternum there was no fat and the marrow was rich in cells. Stoccarda (1915) examined the marrow in the flat bones of the skull in the course of an investigation of the sphenoido-occipital synchondrosis in a number of cretins. He stated that the marrow in the limb bones of cretins is fatty. In the sphenoid and occiput he found mixed fatty and cellular marrow, with less active marrow than in normal controls. Rich red marrow

was present in the bones of the trunk. Askanazy (1927, 1930) stated that hyperthyroidism usually causes no notable change in the bone-marrow, though several observers have described cases with red marrow extending throughout the femur; in hypothyroidism the adipose marrow is increased at the expense of the haemopoietic.

2. *Bone-marrow of animals after thyroidectomy.* Esser (1907) described the post-mortem appearances of the marrow in thyroidectomized rabbits. There is, unfortunately, no note of the interval in time between the thyroidectomy and the examination of the marrow, except in one case, where it was eight days. In the light of other observations this period can hardly be considered sufficient. Tatum (1913) reported the results of autopsies on 25 thyroidectomized rabbits. He found the marrow usually of an inactive fatty type, and says that the erythrocytic centres were exceeded in number by the leucogenetic. Kunde, Green, and Burns (1932) reported that the marrow in their thyroidectomized rabbits, which had developed an anaemia of the simple hyperchromic type, was examined by Bloom. There is no note of the macroscopic appearance. Microscopically, the marrow was fatty in type with finely granular purple-staining masses between the fat cells. In the centres of these there were some groups of blood-forming cells. It was suggested that the marrow resembled that found by Selling in chronic benzol poisoning, and that described by Doan in starved pigeons, that is to say that it was hypoplastic.

3. *Bone-marrow in animals treated with thyroid extract or thyroxine.* Lim, Sarkar, and Graham Brown (1922) investigated the effect of feeding with thyroid on the bone-marrow of normal rabbits of different ages. They found little change in the red-cell count in the sixteen days over which observations were made. In the marrow they found an increase in the cells of the polymorphonuclear series and of the erythroblast series. The latter was not seen in the youngest age group, but the examination in this group was made after only four or five days of thyroid feeding. They considered that their results showed that the thyroid hormone had a stimulating effect on haemopoiesis. Kunde, Green, and Burns (1932) found histological evidence of increased marrow activity in the bone-marrow of normal rabbits treated with large doses of thyroid. The marrow was less fatty than normal, with an increase of red cells, many eosinophils and myelocytes, and a few stem or reticular cells. Power (1934) gave detailed accounts of the marrow of normal rabbits treated with weekly injections of thyroxine over long periods. He found that the marrow at first was increased in bulk and darker red than normal in colour. The proportion of haemopoietic cells was greatly increased and the fat spaces were diminished. The hyperplasia was especially of the red-cell precursors, basophilic mononuclears, and normoblasts. After long periods of injections the vessels were greatly engorged, but there was a scarcity of haemopoietic cells; those present had pyknotic nuclei, and large basophilic early erythroblasts were absent.

*Discussion.* The observations of Langhans, Maresch, Dieterle, and Stoccada

indicate that there may be less red marrow in the bones of cretins than would be normal for their age. It is not known whether these subjects were anaemic, but the observations of Wälehli (1922) and of Parsons (1938) show that most cretins are anaemic, and those of Franklin (1934) show that their anaemia may exactly resemble that described here as the simple hyperchromic type. Observations on experimental hypothyroidism in animals are in agreement in showing that there is a hypoplasia of the red-cell forming elements, with the exception of those of Esser (1907). It seems likely that this discrepancy may be due to the fact that Esser's observations were made soon after thyroidectomy, and before hypoplasia of the marrow had had time to appear.

The scanty evidence available from the examinations of human material and the experimental observations on animals therefore agree in suggesting that the bone-marrow in hypothyroidism is hypoplastic. It is unfortunate that there are no post-mortem records of the bone-marrow in cases of untreated myxoedema. The technique of sternal biopsy was not in use when the observations in this paper were made, but it is questionable whether the examination of sternal-marrow would help to elucidate this question. It is as likely as not, if there is hypoplasia of the marrow in the simple hyperchromic type of anaemia, that this takes the form of a diminished total amount of marrow that is qualitatively normal. In cases with an added deficiency, evidence of a normoblastic or megaloblastic hyperplasia would be expected. The observations of Power on the condition of the bone-marrow in experimental hyperthyroidism in rabbits are the most complete and satisfactory. They show that there is at first a considerable increase in haemopoietic activity, corresponding to the erythrocytosis observed in the peripheral blood count. Later the vessels of the bone-marrow are engorged, but there is a scarcity of haemopoietic cells; and this usually corresponds to an anaemia. There is nothing in the observation of the other authors that differs seriously from those of Power. It seems likely that the marrow described by Kunde, Green, and Burns (1931) corresponds to that seen in the later stages of Power's observations.

#### *Summary of Clinical and Experimental Observations*

The more important observations on the effects of thyroidectomy and thyroid feeding in normal animals and non-myxoedematous human subjects may be summarized as follows:

(1) Thyroidectomy in animals, according to most observers (Esser, 1907; Scherman, 1930; Kunde, Green, and Burns, 1932; Sharpe and Bisgard, 1936), leads to the development of a moderate anaemia. Fellingner and Pfleger (1936) alone were unable to confirm this finding in fully grown animals, but found that adult thyroidectomized animals were more anaemic than were normal controls after a standard bleeding. The anaemia reported by Kunde, Green, and Burns (1932) in young thyroidectomized rabbits exactly resembled

that described here as the simple hyperchromic type of anaemia in myxoedema. Schermann (1930) alone reported the finding of anisocytosis, poikilocytosis, polychromatophilia, and the presence of some erythroblasts in the blood of animals after thyroidectomy.

(2) Total thyroidectomy in non-myxoedematous patients with heart disease is followed in the majority of cases and in the course of several months by a slightly hyperchromic and slightly macrocytic anaemia of moderate severity (Stern and Altschule, 1936). This anaemia also exactly resembles that described here as the simple hyperchromic type in spontaneous myxoedema.

(3) The administration of thyroid by mouth or thyroxine by injections to normal animals leads to an erythrocytosis lasting some weeks and subsequently to an anaemia. There is good evidence that the erythrocytosis is associated with increased activity of the bone-marrow, and the marrow picture corresponding to the subsequent anaemia is described, though the mechanism by which the anaemia is produced is unknown (Kunde, Green, and Burns, 1932; Power, 1934).

(4) Increased erythropoiesis can also be produced in rabbits by repeated subcutaneous injections of thyreotropic hormone, provided that the thyroid gland is intact (Thaddea and Waly, 1934).

(5) Thyroid administration in non-myxoedematous human subjects has three effects:

(a) After single doses of thyroidin (0.1 to 0.2 gm.) by mouth there is a small transient erythrocytosis (Zondek, 1932; Zondek and Kaatz, 1936), which can most simply be explained as due to the passage of red cells from the red-cell depots into the circulation.

(b) After continuous administration of therapeutic doses (4 to 8 gr. daily of thyroid) for several months there is first an increase and then a decrease in the red-cell count and haemoglobin percentage (Hoskins and Jellinek, 1932). Comparison with similar observations on the effects of the feeding of thyroid to animals suggests that the erythrocytosis in this case is due to an actual increase in haemopoiesis, and that the subsequent decrease in red cells and haemoglobin is due to a secondary effect, possibly an exhaustion of the supply of maturation factors or a disturbance of gastric function.

(c) With larger doses both the immediate and the delayed effect may be absent, or there may be in each case a decrease in red cells and haemoglobin.

(6) It has been claimed that the thyroid gland takes a direct part in the production of polycythaemia at high altitudes and in regeneration of the blood after haemorrhage and in anaemias. Mansfeld (1913) reported the absence in thyroidectomized animals, taken to an altitude of 1,015 metres, of the polycythaemia that is observed in normal animals under these conditions, and interpreted this as showing that the thyroid takes a direct part in the production of polycythaemia at high altitudes. There is no note in the paper of the interval between thyroidectomy and the observations on the blood. The average red-cell count of the group of animals taken to an altitude was 5.3 millions at the beginning of the observations, and the average red-cell

count of a control group was 5.4 millions. It seems, therefore, that the observations were made soon after thyroidectomy, and before the usual anaemia had developed. It would be said on the hypothesis of this paper that these animals had an erythron larger than they needed, and in these circumstances the absence of polycythaemia at an altitude of 1,015 metres might be expected. Mansfeld (1913) also found that blood regeneration in animals poisoned with phenylhydrazine took place more slowly if they were thyroidectomized than if they were normal. Fellingner and Pfeleger (1936) reported a similar retarded regeneration in animals made anaemic by bleeding, or by injections of gas gangrene toxin, which was considered to damage the bone-marrow. Regeneration could be restored to normal if the animals were treated with thyroid before they were made anaemic.

It is not necessary to suppose that the thyroid takes any direct part in blood regeneration in order to explain these results. The stimulus to regeneration in any kind of anaemia is the state of oxygen deficiency produced. This stimulus is smaller in animals with a diminished consumption of oxygen after thyroidectomy than in normal animals, and with a smaller oxygen deficiency stimulus slower blood regeneration would be expected.

*Note on the Use of Thyroid in the Treatment of Anaemias*

It has been claimed at different times that thyroid medication is of value not only in the treatment of anaemia in association with hypothyroidism, but also in the treatment of pernicious anaemia, aplastic and 'pseudo-aplastic' anaemia, secondary anaemias, and other blood diseases (Hoskins and Jellinek, 1932; Damblé, 1933; Fellingner and Pfeleger, 1936). In anaemia in hypothyroidism thyroid can be given most conveniently and economically as Thyroideum (B.P.) by mouth. Few patients with spontaneous myxoedema need more than 3 grains a day. To increase the dose up to the limit of the patient's tolerance does not appear to hasten the repair of the anaemia. The hypochromic type of anaemia should be treated with adequate doses of an iron preparation in addition to thyroid, and the Addisonian hyperchromic type with adequate doses of a liver or stomach preparation in addition to thyroid. Diminished metabolism may be present without the distinctive clinical features of myxoedema, and many patients with idiopathic hypochromic anaemia have an appearance not unlike that of myxoedema. The blood-cholesterol and basal metabolic rate should, therefore, be determined in doubtful cases. There is no rational basis for the administration of thyroid preparations in any variety of anaemia unless there is clinical evidence of hypothyroidism or there is a diminished basal metabolic rate. The latter should be suspected in patients with the pernicious type of anaemia who are treated with adequate doses of a potent preparation but have a reticulocyte response which falls short of the expected maximum. In aplastic anaemia the bone-marrow is already failing to respond to the stimulus of oxygen lack and it is useless artificially to increase this oxygen lack by the administration of thyroid.

*Discussion*

1. *The role of the thyroid in erythropoiesis.* The hypothesis that has been developed in this paper appears to explain the available clinical and experimental observations more satisfactorily than other hypotheses have done. If it be correct, there is a state of oxygen surfeit in the simple hyperchromic anaemia of myxoedema, so that the bone-marrow atrophies; whereas in the other types, as in all deficiency dyshaemopoietic anaemias, there is a state of oxygen lack and hyperplasia of the bone-marrow. This difference explains most of the anomalous features that were noticed in the description of the simple hyperchromic type of anaemia.

The extreme slowness of the repair by thyroid of this type of anaemia and the absence of a reticulocyte response are accounted for by the fact that the bone-marrow is in a state of partial atrophy; whereas in the other types the bone-marrow is in a state of normoblastic or megaloblastic hyperplasia, so that a reticulocyte response and a rapid repair of the anaemia follow treatment with thyroid and the missing maturation factor. A rapid, but temporary, repair may also follow treatment with the missing factor alone.

It is now possible to put a reasonable interpretation on the findings in Case 7 (Fig. 10). When first seen she had an iron-deficiency anaemia, modified only in respect of the size of the red cells by the co-existence of myxoedema, and it may reasonably be assumed that her bone-marrow was in a state of normoblastic hyperplasia. When she was treated with iron her blood count increased steadily and rapidly to within the normal range. As, however, she was myxoedematous, the attainment of a normal blood count meant that she was in a state of oxygen surfeit. Her bone-marrow, therefore, began to atrophy and she began to develop an anaemia of the simple hyperchromic type. When this was treated with both iron and thyroid the response was then extremely slow, presumably because the bone-marrow had atrophied to some extent and had once more to increase in amount. The clinical findings can be reasonably explained on this hypothesis. On the alternative hypothesis that thyroxine is needed in the bone-marrow as a maturation factor, it is necessary to explain why the repair of the anaemia is rapid when there is a dual deficiency and both the missing factors are supplied, but extremely slow when there is a single deficiency and the one factor missing is supplied.

Another peculiar feature of the simple hyperchromic type of anaemia is that it is never of more than moderate severity. The lowest figure for percentage of haemoglobin in all the cases on record is about 60 per cent., that is to say, the percentage of haemoglobin is not reduced by more than 40 per cent. It is interesting, therefore, that the total consumption of oxygen after complete thyroidectomy is also reduced by about 40 per cent. If these facts are directly related, one may ask why the degree of reduction in haemoglobin is not related to the degree of reduction of the basal metabolic rate in every case. It has, however, been suggested that adaptation to a diminished need for oxygen may take place by diminution in the cardiac output, or by atrophy of the erythron, or by a combination of the two. If this be the case, a direct

relationship between the degree of reduction of oxygen consumption and haemoglobin percentage need not be expected.

The effects of the thyroid on haemopoiesis are not confined to erythropoiesis. In the cases of myxoedema recorded here a leucopenia with a relative lymphocytosis was the usual finding. Campbell found a similar result in most of the animals in which the white cells were examined when atrophy of the erythron had resulted from exposure to an increased tension of oxygen in the inspired air. This matter needs further investigation, but it is possible that the hypothesis suggested here will be found to explain the role of the thyroid in leucopoiesis and in the production of platelets.

If the erythron is atrophied in hypothyroidism it might be expected that it would be hypertrophied in hyperthyroidism. An erythrocytosis has occasionally been reported in cases of Graves' disease (Crotti, 1918; Zondek, 1922; Askanazy, 1927), as has an increase in the amount of haemopoietic marrow, but in the large majority of cases a normal blood count or a moderate hypochromic anaemia is present (Plummer, 1918; Jackson, 1931). Moldawsky (1928) reported the finding of an increased reticulocyte count in cases of Graves' disease, but the counts of 5 to 16 per thousand which he found would now be considered within the range of normal.

Observations on non-myxoedematous patients (Hoskins and Jellinek, 1932) and on normal animals (Kunde, Green, and Burns, 1932; Power, 1934) have shown that hyperthyroidism produced by feeding with thyroid or by injections of thyroxine does cause an erythrocytosis, but that this is temporary and is succeeded by an anaemia if the hyperthyroidism is maintained. In view of these observations, the absence of any evidence of hypertrophy of the erythron in the great majority of cases of hyperthyroidism does not seem to be a serious objection to the hypothesis that is being considered. The condition of the bone-marrow corresponding to the anaemia produced in animals by prolonged treatment with thyroxine has been described (especially by Power, 1934), and it would be interesting to know whether this picture is at all similar to that of the bone-marrow in patients with anaemia in association with Graves' disease.

Changes in the rate of oxygen consumption may be present without the distinctive features of myxoedema or Graves' disease, and these, too, might be expected to lead to changes in the size of the erythron. In Case 2, described by Snapper, Groen, Hunter, and Witts (1937), as one of a series of patients with hypopituitarism and diminished basal metabolism, but without myxoedema, the anaemia appears to be of the type described here as the simple hyperchromic type, rather than a gastrogenous deficiency anaemia. It is usually assumed that the increased basal metabolic rate which is found in cases of polycythaemia vera (Bliss, 1928; Du Bois, 1936) is secondary to increased erythropoiesis. It seems possible, however, that the reverse is the case, that increased metabolism is the primary disorder and increased haemopoiesis the secondary one. This would bring the aetiology of polycythaemia vera into line with that of the secondary polycythaemias.

2. *The physiology of erythropoiesis.* Witts (1931) has remarked that the pathology of the erythron remains to be written, and it may be added that much the same is true of its physiology. Boycott (1929) discussed the variations in the size of the erythron which take place under different conditions of supply of oxygen to the tissues, and concluded that the normal condition

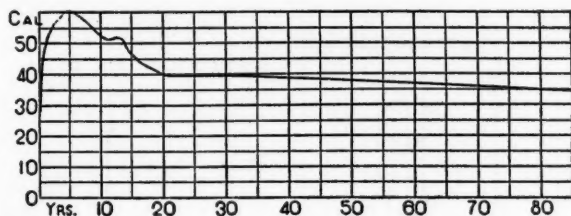


FIG. 14a. Curve showing the level of metabolism at different ages. The results are expressed in terms of calories per hour per square metre of surface area (from Aub and Du Bois, 1917).

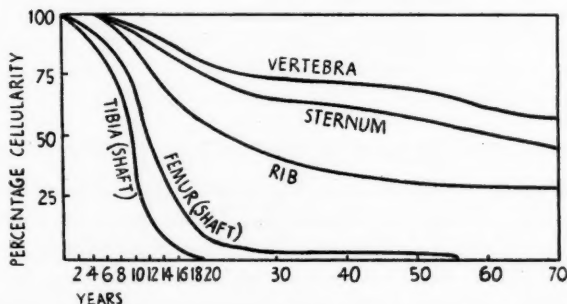


FIG. 14b. Curves showing the amount of cellular red marrow in different bones at different ages (Whitby and Britton, 1937. From the data of Custer and Ahbfeldt, 1932.)

of the blood or the normal size of the erythron depends on the tension of oxygen in the inspired air. If the hypothesis of the present paper be correct, this is but one factor, and the consumption of oxygen by the tissues is another. The normal size of the erythron depends on a balance between these two factors. When either of them is altered there is a compensatory change in the size of the erythron, unless an adequate compensation can be maintained by a change in the cardiac output alone.

It is possible, then, to give a reasonable explanation for the recession of the red marrow up the cavities of the long bones during growth. The rate of metabolism of an animal varies inversely with its size, so that its rate of metabolism decreases as it grows. If we can assume that the volume of the marrow cavities bears a direct relationship to the total size of an animal, it would be expected that the erythron would grow smaller in relation to the total size as the animal grows, and would come to occupy less of the available space in the marrow cavities. It is noteworthy that the relatively rapid decrease in the basal metabolic rate of human beings, which occurs in the

period of growth, is followed at about the age of twenty by a slow but continuous decrease throughout life (Fig. 14 a). At the same age the relatively rapid recession of the red marrow up the cavities of the long bones is succeeded by a slow but lifelong diminution in the amount of active marrow (Fig. 14 b).

#### STIMULUS TO ERYTHROPOIESIS

##### DEFICIENCY OF OXYGEN

i. e. balance  
between supply  
and consumption  
of oxygen.  
(Indirectly the  
thyroid and the  
pituitary  
affecting the  
consumption of  
oxygen through  
the action of  
thyroxin and  
thyreotropic  
hormone).

#### ERYTHROBLASTS



NORMOBLAST  
ERYTHROCYTE

#### MATURATION FACTORS

Liver factor

Iron  
Vitamin C  
? Copper

Thyroid and  
pituitary probably  
concerned indi-  
rectly through  
their effects on  
gastric function.

FIG. 15. Diagram to illustrate the role of the thyroid and other factors in erythropoiesis.

In descriptions of erythropoiesis it is usually not sufficiently emphasized that two distinct factors are involved. There is firstly the stimulus to erythropoiesis, which appears always to be in a state of oxygen deficiency. There are secondly a number of factors which are necessary for the normal maturation of the red cells in the bone-marrow, but which cannot themselves stimulate erythropoiesis or raise the blood count in persons who have no deficiency of them. The parts played by the different known factors concerned in erythropoiesis, if the hypothesis suggested here be accepted, are represented diagrammatically in Fig. 15.

This scheme allows for no direct endocrine effect on erythropoiesis. It is possible that there is such an effect, but at present the evidence for it is unconvincing. Alterations in the blood count may occur in endocrine disturbances in at least three ways, in none of which is there a direct endocrine effect on erythropoiesis:

(1) Alterations in the blood count may be due to changes in the water balance, and be, for instance, analogous to the apparent polycythaemia which occurs in the dehydration of Addison's disease.

(2) A liver or iron deficiency anaemia may follow an endocrine dysfunction, and it is probable, as discussed by Snapper, Groen, Hunter, and Witts (1937) in the case of the pituitary, that in these cases the endocrine dysfunction produces a gastric dysfunction and so a gastrogenous deficiency anaemia.

(3) According to the hypothesis of this paper, the endocrine glands may affect erythropoiesis indirectly through alterations in the rate of metabolism.

It would be necessary to exclude these three mechanisms before concluding from alterations of the blood count in endocrine disturbances that the endocrines have a direct effect on erythropoiesis. The many claims made for the existence of direct endocrine effects on erythropoiesis appear extravagant and the existence of such effects has yet to be proved.

### *Summary*

1. Three types of anaemia are found in association with myxoedema :

(a) The simple hyperchromic type. This type is the uncomplicated anaemia of myxoedema. Its characteristic features are described in detail. It is considered to be part of a decrease in the size of the erythron, which takes place in hypothyroidism as a physiological compensation for diminished need of the tissues for oxygen, and to be akin to the anaemia which appears in animals exposed to atmospheres with a tension of oxygen greater than the normal.

(b) The hypochromic type.

(c) The Addisonian hyperchromic type.

These types are considered to be due to alimentary deficiencies of iron and liver factor, respectively. They differ from the corresponding simple deficiency anaemias only in being modified in certain respects by the co-existence of myxoedema.

2. The simple hyperchromic type of anaemia responds slowly to treatment with thyroid alone, in such doses as are found to keep the patient free from symptoms of myxoedema or hyperthyroidism. The hyperchromic and Addisonian hyperchromic types should be treated with thyroid and with adequate doses respectively of an iron preparation or of a potent liver preparation.

3. It is suggested that the normal size of the erythron depends on the rate of consumption of oxygen by the tissues, as well as on the tension of oxygen in the atmosphere; and that this explains the recession of the red marrow up the cavities of the long bones as the animal grows and the rate of metabolism decreases.

4. There is no evidence that thyroxine is one of the factors whose presence in the bone-marrow is necessary for the normal maturation of red cells. It is suggested that the thyroid affects erythropoiesis only indirectly, through its effects on the consumption of oxygen by the tissues and on gastric secretion.

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STAPHYLOCOCCAL INFECTIONS AT SINGAPORE<sup>1</sup>

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*Introduction*

DURING the past half-century the staphylococcus has been subjected to extensive bacteriological study. According to Gay (1935), the humoral transmission of immunity was first accomplished through the medium of the staphylococcus in 1888. According to the same author, Twort first observed the lytic action of bacteriophage when working with this organism. Stookey and Scarpellino (1937) state that van de Velde in 1894 demonstrated that the staphylococcus produced a soluble principle *in vitro*.

On the bacteriological side, notable advances have been made in our knowledge of the staphylococcus dating from the work of Burnet (1929). Staphylotoxin when injected into the skin of rabbits produces necrosis. Burnet (1929) and Dolman (1932) showed that this could be inhibited by injecting an immune serum. The practical applications of this knowledge will be discussed later. Burnet (1929, 1931) found that anatoxin, or formolized toxin, had a high antigenic value and could be used to produce an immune serum. Ramon, Bocage, Boivin, Mercier, Richou, and Defrance (1937a, 1937b), who have made extensive contributions to the literature, have recently introduced a further modification of staphylotoxin by treating the toxin with trichloroacetic acid, and claim to have increased its antigenic power while diminishing its toxicity. More interesting, perhaps, are the recent observations of Downie (1937) and Panton (1937). The latter found that rabbits injected with living staphylococci react afterwards to a dose which is insufficient to produce a lesion in normal animals. The sophisticated reaction of the immune tissues, however, develops sooner and comes to an end more rapidly. Downie injected animals with staphylotoxin and then with living staphylococci; when the antitoxin content of the blood was raised, a lesion very like a boil developed. These experiments probably reproduce fairly accurately the immunological conditions and the lesions found in chronic staphylococcal infections in man.

In 1927 Besredka published his monograph on tissue immunity, and although his 'anti-virus' has not withstood the test of criticism the main argument on which it was based still holds good. Besredka, dissatisfied with the current theories of humoral and cellular immunity as sponsored by Ehrlich and Metchnikoff, turned his attention to the ecology of the organism

<sup>1</sup> Received March 18, 1938.

within the animal host. In the case of infections by the staphylococcus, he emphasized the part played by the skin in infection and in immunity, a part which should have been recognized by physicians long before. Nevertheless, the purely bacteriological outlook predominated and the staphylococcus continued to be regarded as one of a group of organisms which produce diverse pyogenic lesions. Topley and Wilson (1936), discussing the staphylococcus, point out that: 'The reaction of acute inflammation... is a fundamental defence mechanism, which is brought into play in response to a great variety of stimuli; and there are few bacterial species which are not pyogenic. . . .' While there are, no doubt, numerous organisms capable of producing an acute abscess on injection, in natural infection the staphylococcus is the organism which gives rise to the common boil and its associated symptoms.

On the clinical side, Ryle (1936) has made a notable contribution in his observations on staphylococcal fever. His account of its natural history is much more than a description of a bacteriological infection. It is a clinical picture of a disease which, from its primary lesions in the skin, tends to metastasize in the internal organs, but in all its stages has a constant tendency towards localization.

While the distribution of the staphylococcus, like that of the streptococcus, seems to be universal, the relative prevalence of their respective lesions seems to be governed by climatic influences which have not yet been defined. In the tropics streptococcal lesions are, on the whole, comparatively rare. Scarlatina is very rare, erysipelas is seen more frequently, but is not so common as in temperate climates, and acute rheumatism and its sequelae are only occasionally seen. Staphylococcal lesions, on the other hand, are, in our opinion, seen much more often than they are in temperate climates. Indeed, there are one or two special manifestations of staphylococcal infection which seem to be peculiar to warm climates.

#### *Boils and Associated Lesions*

The boil is the typical and very often the initial lesion produced by the *Staphylococcus aureus*. It is considered that infection begins in a hair follicle and is usually confined to the corium. A carbuncle, on the other hand, is located in the subcutaneous tissues, and its association with diabetes is usually explained on the basis of lowered resistance. In the healthy subject it is supposed that the invading organisms are held up at the level of the hair follicles by abscess (boil) formation, whereas in the diabetic the staphylococcus penetrates to the subcutaneous tissues—perhaps *via* the sweat glands—before the threshold of reaction is reached.

Ryle's conception of staphylococcal fever as a clinical entity includes initial skin lesions together with metastases in the internal organs. This syndrome is now well recognized in the case of perinephric abscess. In other cases of deep suppuration due to *S. aureus*, e.g. in lung abscess and pyomyositis, it is not always possible to establish a history of primary skin

lesions, but, as Ryle points out, an antecedent sty or furuncle might easily be missed. We are satisfied that a large proportion of these abscesses are metastatic in origin and that staphylococcal fever is a very definite syndrome. Sometimes, however, the skin lesions are predominant, and there is the type (see Case 1) in which these alone seem to account for the fever. In other cases, and this is perhaps the typical syndrome, boils are followed by metastatic internal abscesses. There is a third type of case in which primary skin lesions are negligible or absent. This third group is important because it includes many cases of lung abscess and also some of those deep abscesses in the muscles which have been described under various names—pyomyositis, tropical myositis, colonial myositis, etc.

There are many variations from the typical picture of staphylococcal fever as outlined by Ryle. Some of these are of such magnitude as to suggest that we are dealing with a different aetiological agent, or at least with a different strain of *S. aureus*. In this study we have chosen for illustration only those cases which have some bearing on the unity of staphylococcal infections as a whole. Many of them are interesting on account of the problems they present in diagnosis and treatment, but the primary object in this work was to see if there were not some clinical, as well as bacteriological, connecting link between all these diverse manifestations of infection. The fact that epidemics of a special form of staphylococcal infection occur at times, and that in such epidemics children and adults of various races are infected, suggests that variations in the 'soil' alone cannot account for the diversity of lesions. On the other hand, the tendency to form lesions in the skin, the tendency to metastasize and to give rise to localized lesions even after metastasis, are features which are traced in all the varieties of the infection which are described here or have been recorded.

### Case Reports

The first case to be described is one of boils—staphylococcal fever without metastasis.

*Case 1.* A. C., European male, aged 35 years, admitted to the General Hospital, Singapore, on 11 July 1936. He had had fever and malaise for three days before admission. On admission, black necrotic lesions were noted on the right leg, left thigh, and right lower jaw. He said that they came up as pimples. His white-cell count on 12 July showed 3,800 cells per c.mm., of which 58 per cent. were polymorphs, 32 per cent. lymphocytes, 2 per cent. eosinophils, and 8 per cent. monocytes. The next day a fresh crop of pustules erupted, from one of which *S. aureus* was cultured. Blood-culture was negative for the enteric group of organisms. The temperature, which was 101° F. on admission, lasted 8 days and fell by lysis. The pulse-rate never exceeded 80 per minute. He was discharged after a fortnight in hospital, but an occasional boil came up for the next three weeks. During this time, although he was able to carry on with his work, he was by no means in perfect health. The disease, apart from the fever, may be reckoned to have lasted six weeks.

During the first few days the necrotic lesions suggested the possibility of Japanese river fever. Later, the white-cell count suggested typhoid. Ryle mentions the presence of a leucocytosis from the beginning as an important point in the diagnosis from typhoid fever. In our experience, there may be no significant deviation from normal in the white-cell count during the stage of boils. Later, with the advent of metastasis, leucocytosis occurs. In the early stages the similarity to typhoid may be very close—remittent fever, slow pulse, leucopenia or normal white-cell count, 'toxic' appearance—and if the case is further complicated by recent T.A.B. inoculation the picture can be very confusing indeed.

The second case illustrates the long duration of this disease, the difficulties in exact diagnosis, and the great strain thrown on the resources both of the patient and his doctor.

*Case 2.* A. B., European male, aged 36 years, was first seen at 'A' Hospital as an out-patient. He complained of having felt rather 'seedy' for a fortnight and of having had boils. He had had ten years' service in Malaya and had only recently returned from home leave in Europe. He was admitted on 29 June 1936, with a large boil on the left thigh and several smaller ones on the rest of the body. His temperature was 100.2°F. on admission, pulse-rate 98 per minute. Microscopical examination of the blood for malarial parasites, of the stools for ova and protozoa, and of the urine revealed no abnormality. Physical examination revealed nothing of note beyond the boils. He had had a T.A.B. inoculation within the previous three months. The blood Wassermann and Kahn tests taken at a later stage were negative. The main events connected with the case may be set out in chronological order as follows:

29 June: Admitted to hospital. 2 July: Pain in right hip and thigh; limitation of extension of right hip. 3 July: White-cell count, 11,000 per c.mm.; polymorphs, 80 per cent. 5 July: Widal test: serum agglutinated paratyphoid A in 1/50 (R.T. 12), paratyphoid B in 1/50 (R.T. 8), negative to typhoid (H and O). 10 July: Stool and urine cultures reported negative for enteric group of organisms; boils still appearing. 11 July: Tumour palpated deeply in right iliac fossa, and thought to be connected with ilium. Diagnosis—staphylococcal or (para)typhoid abscess; white-cell count, 17,000 per c.mm.; polymorphs, 78 per cent.; blood sent for culture reported negative for organisms after seven days' incubation. 12 July: Widal test: paratyphoid A agglutinated in 1/125 (R.T. 20), negative to typhoid, paratyphoid B, and C (H and O). 16 July: White-cell count, 14,000 per c.mm.; polymorphs, 80 per cent. 17 July: Tender mass felt high up on the right on rectal examination; X-ray of pelvic bones showed no abnormality. 18 July: Operation (ether convulsions occurred); an extra-peritoneal exploration was carried out; the surgeon felt a lump in the iliacus which, on exploration, revealed no pus or sequestrum. 28 July: Blood culture reported negative after nine days' incubation; *S. aureus* isolated from pus from operation wound. 30 July: Still having boils; wound, which has been kept open, still discharging small amount of pus; sequestrum thought to be felt on probing; X-ray findings negative. 31 July: Tenderness in right loin; rectal examination revealed no abnormality; urine showed very few pus cells and a few red cells; no frequency of micturition; culture of urine later showed *S. albus*. 2 August: Swelling and oedema of right loin

extending upwards from crest of ilium, but not as far as costophrenic angle; white-cell count, 8,200 per c.mm.; polymorphs, 74 per cent. 12 August: Swelling of flank more pronounced; operation (ether convulsions again occurred); the original wound was extended upwards; an elongated oedematous mass was found extending upwards into the loin; no pus was found on incising this mass. 21 August: Widal test: negative for the *abortus* group; paratyphoid A still agglutinated in 1/125 (R.T. 20). 28 August: White-cell count, 11,800 per c.mm.; polymorphs, 82 per cent.; urine on microscopical examination showed no abnormality. 29 August: White-cell count, 10,500 per c.mm.; polymorphs, 81.5 per cent. 31 August: White-cell count, 10,400 per c.mm.; polymorphs, 83 per cent.; *S. aureus* cultured from the blood. 2 September: *S. aureus* again reported in blood culture. 3 September: Admitted to 'B' Hospital, still having boils; X-ray again revealed no abnormality in the pelvis or abdomen, but showed signs of infection around some teeth; the temperature was still running 99° to 101° F. and the pulse-rate 96 to 102 per minute. 9 September: Two teeth were extracted, and cultures taken from their roots later showed *Streptococcus viridans* and other organisms, but no staphylococci. 12 September: The temperature came down to normal and did not rise again. 18 September: Further teeth extractions. 9 October: Patient discharged from hospital.

This case provides a good example of prolonged staphylococcal fever. The results of the Widal tests proved somewhat confusing, as they could at no time exclude one of the enteric group of fevers, and the other tests at one time seemed to favour the diagnosis of a Brodie's abscess in the ilium complicated by boils. The blood-culture results are interesting and suggest that a bacteriaemia is not of such grave prognostic import in staphylococcal as it is in streptococcal infections. It will be noted that the blood-culture was not positive until the disease was approaching the end of its natural course. We consider that the case was one of staphylococcal fever with primary skin lesions and an internal metastasis not amounting to abscess formation. The chief importance of the case lies in this diagnosis, because it is a link between the staphylococcal fever of temperate climates and the pyomyositis or deep muscular abscess of the tropics.

#### *Scalp Infections in Chinese Children*

This is probably the commonest manifestation of *S. aureus* infection among the local Chinese population. The disease is commoner among the children of the poor than among the well-to-do. It is seen mostly between the ages of 4 and 18 months. Typically, a well-nourished, rather fractious, Chinese infant is brought in with his head bathed in pus which is pouring from half a dozen boils on the scalp. The cervical, occipital, and submental glands may be enlarged or even suppurating. There may be a few boils or 'septic spots' on the limbs and trunk. It is difficult to arrive at an exact figure for the incidence of these infections, or to assess the part they play as a cause of morbidity among in-patients. In many cases the boils develop during the course of another disease or during convalescence. The classification of diseases in the *International List of the Causes of Death* (1931)

distributes staphylococcal lesions under many headings. To sift out the staphylococcal cases from the hospital records would entail a most laborious piece of work and was out of the question during the time at our disposal.

Dr. Haridas has kindly supplied the following information, which gives some impression of the incidence of the disease in the Children's Ward of the General Hospital, Singapore:

Between 12 July and 12 August 1937, 170 patients were admitted to Ward XIII—the ward for children  $1\frac{1}{2}$  years and under. A census of boils in Ward XIII on 8 July 1937 showed: Total number of infants, 63; age limits, 0 to  $1\frac{1}{2}$  years; cases with boils, 22; racial incidence of boils, Chinese 21, Indian 1. Of these, 19 were admitted for boils, and 3 developed boils after admission. In 10 cases there was a severe eruption of boils, the rest had only a few lesions. In all except three cases the boils were confined to the head region.

The duration of the disease varies considerably in different patients. It bears no constant relation to the severity of the infection or to the state of nutrition of the child. The average case, we would say, clears up in three to four weeks. In the case of children of a year and upwards the general condition is often surprisingly good and the outlook on the whole is bright. In the case of infants, however, enteritis is a frequent sequel and is very often fatal. Dack, Bowman, and Harger (1935) traced a minor epidemic of gastro-enteritis in adults to meat-sandwiches from which they isolated a haemolytic strain of *S. aureus*. They reproduced the symptoms in monkeys by feeding them with veal emulsions which had been previously inoculated with the *S. aureus* isolated from the sandwiches. Blackman (1935) has described a case of acute fatal gastro-enteritis associated with a haemolytic strain of *S. albus*. There were severe lesions in the upper part of the small intestine. He mentions the formation of intestinal casts, erosion of the mucous membrane, and the presence of thrombi in the small vessels. Stookey and Scarpellino (1937), working with staphylococci which they isolated from their own patient, injected staphylotoxin into rabbits and produced, among other lesions, ulceration of the intestines. In view of these observations, it would not be wise to dismiss the possibility of the enteritis in our cases being due to staphylococcus or its toxins. Actually, we sent the stools for culture from some typical cases, but the staphylococcus was never isolated.

Metastasis may occur by way of the blood-stream or lymph channels. Direct spread along the surface of the skin from one hair follicle to the next also occurs, and this seems to be enhanced by the application of wet dressings, whether these dressings are antiseptic or not. The prognosis in the case of lymphatic spread is, on the whole, good. The infection is held up by the regional lymph glands, and secondary abscess formation occurs. In the case of haematogenous spread the prognosis, although not invariably bad, is always grave.

*Case 3.* K. K. J., Chinese male infant, aged 5 months, admitted to the General Hospital, Singapore, on 16 February 1937. There was a history of boils on the head for a month before admission. He had had a cough for a

similar period. Three days after admission a large abscess was opened in the left axilla and 10 ounces of pus evacuated. Crops of boils continued to come out and abscess formation occurred in various regions, on the buttocks, posterior part of the scalp, and over the spine. Enteritis set in, and the child died a fortnight after admission. *S. aureus* was isolated from the axillary abscess, but not from the stools. A white-cell count on 18 February showed 29,000 cells per c.mm., of which 53 per cent. were polymorphs.

*Case 4.* A male Chinese infant, aged 4 months, the son of comparatively well-to-do and educated parents, was admitted to the General Hospital, Singapore, on 16 May 1937, with swelling of the upper and lower eyelids on the left side. There were a few boils on the scalp. The father said that the child had been having boils on the head for the previous month. He had squeezed some of them and applied antiseptic dressings. The swelling in the eyelids developed on 15 May, on which day fever was noted for the first time. On the next day—the day of admission—the upper eyelid was incised. The condition was diagnosed as orbital cellulitis. The temperature rose to 100.5° F. the next morning, and oedema appeared at the root of the nose. The right eyelids became swollen on the same day and a purulent discharge began to pour from the left nostril. *S. aureus* was later isolated from this source. The general condition of the child became rapidly worse, signs of consolidation appeared in the right lung, the temperature varied between 103° and 104° F., and death occurred on 21 May.

In Case 3 the prognosis was bad from the beginning. The child was puny and weak, and as soon as enteritis set in the chances of recovery were remote. In Case 4 the child was well nourished and well cared for. The focus in the lung might have been effectively localized and the pus coughed up in due course. It was probably the infection in the ethmoid that determined the fatal issue. It is often the anatomical position of these secondary abscesses, rather than the resistance of the patient, that determines the issue in such cases.

What determines the high incidence of boils on the scalp in Chinese children is a problem to which we have devoted attention. Malnutrition is common in the East and is, no doubt, an important factor in some cases. But this alone could not account for the high incidence in the Chinese, especially as many cases occur in well-nourished children, in whom evidence of malnutrition would be very difficult to demonstrate. If malnutrition were the chief factor one would expect a higher incidence among the Indians. Since the Chinese discarded the habit of wearing pig-tails, the pendulum of fashion has swung in the opposite direction, and it is common, especially among the coolie class, to find close-cropped, or actually shaven, scalps. This is especially the case in children, where it has become practically a universal custom to shave the scalp or cut the hair close with a mechanical hair-cutter. We believe that it is through the small abrasions which inevitably result from such procedures that infection occurs.

#### *Pemphigus Contagiosus*

A bullous eruption associated with *S. aureus* has been described under various names: pemphigus contagiosus, pyosis masoni, pyosis corletti. Manson (1898) described it in the first edition of his *Tropical Diseases*, and noted

that it was common in the Straits and China coast. He refers to Singh's (1895) description of the condition in India. Although common in the tropics, and especially in the East during the monsoons (Buist, Bhatnagar, and Carr, 1934; Eccles, 1932), Sequeira (1927) mentions that it has been recognized in small epidemics in British hospitals. Poole and Whittle (1935) described an epidemic among children which was traced to a nurse suffering from a small perionychial whitlow. *S. aureus* was isolated from all their cases and they considered this organism responsible for the disease. This view was questioned by Adamson (1937), who suggested that *S. aureus* was merely a contaminant and that a streptococcus was the aetiological agent. His argument is a weak one and he does not quote personal experiences. It is almost impossible to believe that *S. aureus* should be isolated so often in pure culture if a streptococcus were the causal organism. Castellani and Chalmers (1919, 1923) state that the lesions are caused by *S. aureus*. Cunningham (1924) isolated streptococci as well as staphylococci, but the rapidity with which primary staphylococcal lesions become contaminated with streptococci has often been noted. According to Castellani and Chalmers, the condition is often followed by boils. Carter and Osborn (1936) state that one of their fatal cases was complicated by abscesses. We have met two instances of the disease in Europeans.

*Case 5.* European female infant, aged 5 months, admitted to the General Hospital, Singapore, in December 1936. She had small bullae on the trunk and limbs. The lesions were multiple, but not confluent; some were purulent, but most of them were clear; many were ruptured. The general condition was quite good, this in spite of the fact that she had already been admitted to hospital on two previous occasions for enteritis. The father informed us that there was an epidemic of the disease in progress on the rubber plantation where he lived, all the native children being affected. The children, he said, did not appear to suffer much from the effects of the condition. *S. aureus* was isolated in pure culture from one of the blisters in our case. The condition cleared up in a week.

*Case 6.* European female, aged 38 years, admitted to the General Hospital, Singapore, on 18 May 1937 for severe subtertian malaria. The patient was very ill on admission. On account of persistent vomiting, quinine had to be given by injection for the first three days. On the third day after admission she developed bullae about the right axilla and on the arm, breast, and neck of the same side. Successive crops of bullae appeared daily for ten days. Fluid taken from a blister yielded *S. aureus* in pure culture. The condition lasted a fortnight.

The generalized type (Case 5) is usually referred to as pyosis corletti. Pyosis mansonii (Case 6) is more localized and occurs about the axillae and genito-crural region. Although an occasional fatality has been reported in European epidemics, as in Poole and Whittle's cases, the disease is a very mild one in the tropics. Its interest rests partly in the diagnosis and partly in its association with boils. Both Manson and Castellani, and Chalmers, say that it is occasionally followed by boils. We have seen a vesicular lesion

occasionally in cases of boils on the scalp in Chinese children. In one of Stookey and Scarpellino's cases the condition started as a vesicular lesion and progressed to severe ulceration in the groin, axilla, and neck. They gave staphylococcal antitoxin to this case, and thought that it produced excellent results. It seems, therefore, that the staphylococcus responsible for this condition can, at least, give rise to other types of skin lesion. We have not been able to find references in the literature to any internal metastasis following these lesions or the subsequent boils or abscesses.

#### *Staphylococcal Pneumonia and Lung Abscess*

The part played by *S. aureus* in the causation of lung abscess is difficult to assess. It would probably be true to say that, next to the skin, the lung is the tissue which is most susceptible to invasion by the staphylococcus. In those cases of acute, fatal, disseminated lesions abscesses are almost invariably found in the lungs. This has been noted not only in our own cases, but in those described in the literature on the subject.

Smith (1935) and Macgregor (1936) have recently described cases of staphylococcal pneumonia in children. The pathological changes which they found included patchy consolidation and, in almost all cases, abscess formation. In many cases the abscesses were miliary; in most cases there was involvement of the pleura, the exudate being sometimes blood-stained and often purulent. In three of Macgregor's cases there was pyopneumothorax. No primary skin lesions are mentioned by these authors. We have found similar lesions in many of our own cases *post mortem*. Reimann (1933) has described a series of cases of staphylococcal pneumonia; he gives a good review of the condition and considers that about 7 per cent. of all cases of pneumonia are staphylococcal in origin. Abscess formation, with or without empyema, seems to be the characteristic lesion in staphylococcal 'pneumonia'. Even in the most fulminating cases there is always some attempt at localization, often in the shape of miliary abscesses. Maxwell (1934) has reviewed the aetiology of lung abscess and described the pathological findings in a series of his own. His own series, and those of others whom he quotes, demonstrate the fact that operations on the upper respiratory tract are not responsible for such a high percentage of lung abscesses as was previously thought to be the case. In his series of cases he found *S. aureus* the predominant organism, whether the cultures were taken from the heart blood or from the abscesses.

In Malaya the incidence of lung abscess is high. It is not proposed to discuss the diagnosis of the condition here, but it may be pointed out that if all pneumonias which still run a high temperature after the tenth day were radiographed, a high incidence of lung abscess would be disclosed. Many of these abscesses are secondary and are to be traced to causes similar to those which operate in temperate climates. In addition, there is the important abscess which is secondary to amoebic abscess of the liver, but it

is the primary—often solitary—abscess of the lung which concerns us here. There are strong *a priori* grounds for the belief that the staphylococcus is responsible for a high percentage of these 'primary' abscesses. In the first place, we have already noted the predilection of the staphylococcus for the lung. Secondly, in so-called staphylococcal pneumonia we see the tendency to abscess formation. In the third place, in all Reimann's cases, in 90 per cent. of Macgregor's cases, and in many of Maxwell's cases, as well as in some of our own cases, *S. aureus* has been isolated from the sputum, from the actual lesions, or from the heart blood. Fourthly, the staphylococcus has a definite tendency to form one or more large abscesses, as seen in the case of pyomyositis to be described below. It is worth noting too that 23 per cent. of Sayers' (1930) cases of pyomyositis had pulmonary lesions as well; he speaks of 'some consolidation . . . resembling a low grade pneumonia'. Similarly James (1931) and Buxton (1928) both mention lung complications, and possibly some of their cases had that small central abscess the existence of which can only be definitely proved by X-ray. Such abscesses may not be coughed up; they often undergo slow resorption. We have not made it a rule to send the sputum for culture in cases of lung abscess, and we could not reasonably expect a positive culture for staphylococcus in those cases which come in after the third or fourth week. Contamination occurs quickly and *S. aureus* might easily be outgrown by other organisms in culture. In the following two cases it was isolated:

*Case 7.* Chinese male infant, aged 28 days, admitted to the General Hospital, Singapore, on 30 January 1937. The child was very ill on admission, dyspnoeic, and cyanosed. He died on 2 February. Post-mortem examination revealed early pericarditis and two large abscess cavities in the right lung with overlying empyema. A culture from the right lung gave *S. aureus*.

*Case 8.* Chinese male, aged 34 years, admitted to the General Hospital, Singapore, on 26 November 1936. He had had fever and rigors for three days before admission. His temperature was 102° F. on admission and his pulse-rate 92 per minute. No physical signs could be made out in the chest for the first three days in hospital. Hookworm ova were found in the stools; no malarial parasites in the blood. A white-cell count on 3 December showed 14,800 cells per c.mm., of which 84 per cent. were polymorphs. He ran a remittent temperature with daily rigors for ten days. On 4 December he coughed up some foul-smelling sputum, and signs of consolidation and fluid were present on the right side. The sputum yielded *Pneumococcus*, *Streptococcus viridans*, and *Staphylococcus aureus* on culture. He died on 5 December. *Post mortem*, a large abscess was found in the upper part of the right lower lobe. The right pleural cavity contained about 10 oz. of blood-stained fluid. There was a small abscess in the left lower lobe. The liver was enlarged, but did not contain pus.

#### *Pyomyositis*

Deep suppuration in the muscles has been recognized as a clinical entity in the tropics for many years and has been described under various names.

Sayers (1930) found the condition very common in Samoa and associated it with staphylococcal infection. Owing to the high prevalence of filariasis in this region, however, it was afterwards suggested that the abscesses might be filarial in origin. Buxton (1928) gave an account of the condition in Samoa, and in discussing the aetiology of the condition rejected filariasis as a cause. He pointed out that the incidence of filariasis in the Samoans was 36.1 per cent. Microfilariae were not found in all the cases of pyomyositis, and furthermore, the sex incidence was against filariasis, 36 males being found among 41 cases of pyomyositis. *S. aureus* was isolated in 24 cases which were examined bacteriologically, and in 21 of these it was present in pure culture. Apart from the fact that microfilariae were found in the blood of some of the patients, the only real evidence in favour of filariasis was that a doctor had reported to Buxton the finding of an adult filaria in such an abscess. Bahr (1912) reports a similar finding in an epitrochlear abscess. Sayers (1930) and James (1931) found the condition common in the Pacific islands, and both associated it with staphylococcal infection. In the correspondence following Sayers' article, Manson-Bahr (1930) and Low (1930) stated that they considered that filariasis was at the root of these lesions. Buxton (1930) disagreed with this view, emphasizing the difference in sex incidence between pyomyositis and filariasis. Grace, Grace, and Warren (1932) noted the rarity of the condition in Kingston, Jamaica, where filariasis is uncommon, and contrasted this with the high incidence in those parts of the world where filariasis is more frequently encountered. At the same time they noted that staphylococcal infection was frequent in Kingston. From 100 consecutive cases of abscesses in all regions of the body they cultivated a staphylococcus in 90 cases. Meyer-May and Vaucl (1936) have recently described 12 cases of pyomyositis. *S. aureus* was isolated from seven out of eight cases in which the pus was cultured. These authors also found that their cases showed high agglutinin titres for *L. ictero-haemorrhagiae* and on the strength of this suggest that the latter organism may be in some way responsible for the incidence of pyomyositis.

One of the interesting features of this condition is the fact that the nodes which occur in the muscles do not always go on to suppuration. In fact, Sayers noted that suppurative and non-suppurative nodes might occur in the same patient. In the matter of diagnosis, these cases often present difficulty. In one instance we have seen suppuration in the gluteal muscles mistaken for a short time for tuberculous disease of the hip-joint. In another instance, a fluctuating abscess of the sacro-spinalis in an infant simulated spina bifida. In Case 2 appendicitis, Brodie's abscess, psoas abscess, etc., had to be considered. Disseminated lesions may occur in the viscera. Giblin (1932) described pericarditis in a case, and Buxton thought that one of his patients developed malignant endocarditis.

On the question of whether filariasis or leptospirosis predisposes to this type of lesion, we feel that the onus of proof lies on the authors who postulate those aetiological factors. In Malaya filariasis is rare outside a few

areas where it is endemic. Leptospirosis occurs in small epidemics, usually associated with a particular bathing-pool. Pyomyositis is a common condition and its distribution does not seem to be confined to any particular district. In the cases observed by us, about 30 in all, whenever the uncontaminated pus was sent for culture staphylococci were always grown. In practically all of the cases *S. aureus* was the organism found, but in two recent cases *S. albus* has been reported. The lesions were preceded in some of our cases by boils. In Case 2, for example, the pyomyositis was an incident in prolonged staphylococcal fever. In many cases we were not able to elicit a history of boils or demonstrate any scars as evidence of previous infection. In a recent case in a Chinese a crop of boils preceded the abscesses in the muscles. The patient stated that he had been having boils for a fortnight before admission to hospital. On admission there was one large abscess in the right thigh which yielded *S. albus* on culture.

A feature which deserves more attention in these cases is the absence of glandular involvement. In Buxton's series, where adenitis was present this could be accounted for by the concomitant filariasis. In the cases seen by us glandular enlargement was never noted as a prominent feature. It is doubtful if it would have escaped our observation if it had been present in all cases. It is to be regretted at this stage that we did not pay more attention to the question as, if it could be established that glandular involvement was absent in this type of lesion, it would be a point of considerable significance. This significance we shall discuss later.

#### *Treatment*

It is not proposed to discuss in detail the treatment of all the manifestations of staphylococcal infection. It is easy to visualize circumstances in which the combined skill of the physician and surgeon will be required. A knowledge of the natural course of the disease must form the basis of rational treatment, and such a knowledge is essential for the assessment of the effect of any therapeutic measure.

Generally speaking, there is a marked tendency for the tissues to localize staphylococcal infections. Abscess formation is the natural local response and is very successful in the large majority of cases, whether it is in the shape of a boil, furuncle, or internal abscess. Boils require careful handling. There should be no cutting, squeezing, or detachment of sloughs. Fraser (1936) is emphatic on the subject—*never incise a boil*. Probably the best treatment is to put on a piece of elastic adhesive plaster as soon as the swelling appears. In this way many boils are aborted. Once the boil bursts, it quickly becomes contaminated by other organisms, including the streptococcus. Some of our enteritis cases had that combination of dry, glazed, pointed tongue and diarrhoea which, as Ryle points out, is associated with streptococcal infection. In the case of boils which have already opened

an attempt might be made to limit surface spread. We think this is best accomplished in most cases by calamine lotion which is left to dry on the surface. Crust formation is encouraged by this method.

Deep suppuration comes within the province of the surgeon. Even here, however, we think it is good practice to postpone operation as long as possible. It gives the patient and the surgeon great relief to open a well-encapsulated abscess, and it is a disappointment to both to have an operation for pus which is not there. In those urgent cases in which the tissues fail to localize the infection it is unlikely that the cutting and trauma of an operation will help. Judgement is more important than technique when dealing with *S. aureus*. The surgeon should try and time his interference to the moment at which local response has reached its best effort and where any further increase in the pus would cause the infection to spread along the tissue planes or into a serous cavity.

With regard to drugs, we have no evidence that manganese, tin, anti-staphylococcal serum, or vaccine, to mention some popular remedies, have any beneficial effect over a long series of cases. Whitby's (1936) results with toxoid in chronic skin lesions are no more convincing than, say, Besredka's (1927) results with 'antivirus'. This is hardly to be wondered at, for an active lesion must be in itself a very powerful means of vaccination. MacNeal and Frisbee (1936) make a strong plea for the use of bacteriophage, but here again their results are not impressive. It is, of course, extremely difficult to assess the results of any particular treatment in a condition of this kind. It seems to us that a remedy which succeeds after a long series of other therapeutic measures have failed should not on that account be regarded as specific. From one point of view, the more remedies that have been tried the more chronic the case is, and consequently the nearer to its natural termination. Ramon and his colleagues (1937) have now reported their results in over a thousand cases treated by anatoxin. Recently they have been using an anatoxin prepared with trichloroacetic acid. By adopting the optimum interval between injections, and using this purified, concentrated, trichloroacetic acid anastaphylotoxin, they are satisfied that good results are obtained. Outside France, however, this type of treatment has aroused little enthusiasm. Buchman (1937) studied the effects of toxoid in 38 cases of chronic osteomyelitis. Like other observers, he found that it was possible to raise the antitoxic titre of the serum by repeated injections of toxoid, but he noted no correlation between the serological and clinical results in his cases. For example, a rise in titre (a) did not indicate regression of lesions, (b) did not prevent development of new lesions in 18 out of 38 cases, (c) did not expedite healing of existing lesions, and (d) did not prevent the progression of old lesions. Joyner and Smith (1936) have used antitoxin in the treatment of osteomyelitis. They had three deaths in 13 cases, against an expected mortality of 50 per cent. They think the remedy is worthy of trial, but their series of cases is too small for the results to have much significance.

*Discussion*

We would like to know exactly the part played by the skin in immunity to staphylococcus. Besredka says, 'It is the cutaneous infection . . . that dominates the aetiology of the greatest number of diseases in man caused by the staphylococcus. . . .' He considers that any immunity we possess towards the staphylococcus is somehow connected with the skin. We did think at first that the primary skin lesion was the connecting link between all the staphylococcal infections. Now we are not so sure, but we still feel that we are dealing with a similar, even if not identical, aetiological agent in all the conditions which we have described. Bacteriologists have not yet discovered any certain method of distinguishing the more virulent strains of staphylococcus. Pigment production is not a reliable guide. Among others, Bigger, Boland, and O'Meara (1927) and Pinner and Voldrich (1932) have reported *albus* variants in *aureus* cultures. Burnet (1929) could get a potent filtrate from *albus* cultures.

The nature of the response to specific treatment is interesting from the point of view of the unity of staphylococcal infections. It will be noted in the first place that for the purpose of specific treatment the identity of the staphylococcus of boils with that of osteomyelitis—or meningitis, as in Chabrol's (1937) case—has been tacitly assumed by all observers. It is difficult to say how far such an assumption is justified. We know that differences in the 'soil' and the circumstances of insemination can account for many of the different forms of disease, even when the 'seed' does not vary.

Panton, as has been stated, noted that a smaller quantity of infective agent gave rise to a lesion in the tissues of the immunized rabbit. Burnet (1929) noted that if large numbers of staphylococci were injected into toxin-immune rabbits they died later with extensive suppuration in the kidneys. Is there a parallel between this and the perinephric abscess in man? Buttle (1937), working with a strain of staphylococcus isolated from a case of bovine mastitis, found that 80 per cent. of his animals could be protected against lethal doses of staphylococci for 48 days by the administration of sulphanilamide. Half of the surviving animals, however, showed abscesses in the viscera which yielded staphylococci in culture. This further emphasizes the tendency of the staphylococcus to metastasize and give rise to localized abscesses showing chronic infections. In Downie's experiments it was the lesions in the immunized animals which more closely simulated boils as seen in man. The further observation by Panton that in successive crops of boils the late ones tend to come up and to resolve more quickly than do the initial ones is suggestive. It reminds one of von Pirquet's (1903, 1911) observations on vaccination. An injection of lymph into a vaccinated animal evokes an infiltrated lesion which is rapid in its evolution and quickly disappears. This lesion differs qualitatively, as well as quantitatively, from the vesicular lesions of vaccinia in the uncontaminated animal.

The involvement of the regional glands, when it occurs, suggests that we

are dealing with a primary infection. This is found commonly in Chinese children suffering from boils on the scalp, and occasionally in the early stages in other cases of boils. It is not a prominent feature of pemphigus contagiosus, osteomyelitis, pyomyositis, or lung abscess.

There are many facts, then, to suggest that allergy plays a part in the type of disease which results from staphylococcal infection. In these circumstances, are we justified in injecting substances like toxoid or anti-toxin which we know will increase the sensitivity of the tissues in animals? True, there is a sound teleological basis for each lesion that occurs, but, as already pointed out, the anatomical site of such lesions is often the factor which decides the issue. To increase the sensitivity of the tissues and thus to encourage the development of fresh lesions is theoretically unsound practice. Unless, therefore, the empirical results of specific therapy justify its use, it is hardly to be recommended in treating these infections in man, and the empirical results—outside France—are not by any means impressive. A somewhat similar argument has been put forward by Rich (1936) and others in the case of tuberculosis, but whereas Rich advocated abolition of the tissue hypersensitivity, we are more inclined towards non-interference or to a closer study of the effects of interference. To use Ryle's term, if we knew more about the natural history of these infections we should be in a better position to study the effects of treatment.

Clearly, it is difficult, in our present state of knowledge, to say how far we should regard all these staphylococcal diseases as a single nosographic entity. The uniform histological basis and the sharply defined bacteriological agent give the diverse manifestations of diseases like syphilis and tuberculosis a coherence which is lacking in staphylococcal infections. It may, however, be that the diversity of pathological lesions is accounted for by the difference in reaction of the tissues and the circumstances of insemination.

#### *Summary*

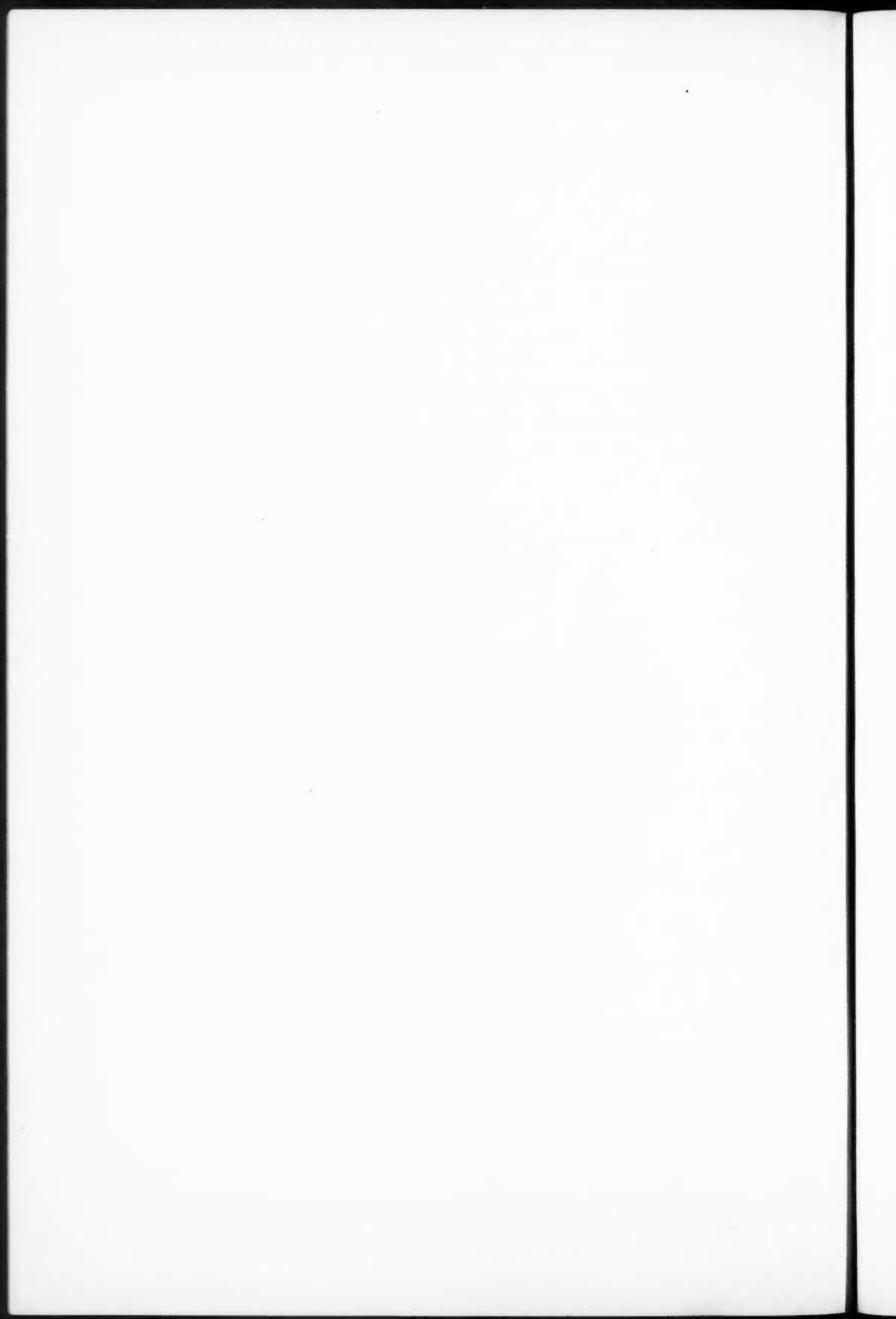
1. A patient may have a few boils without any major constitutional symptoms, fever, or metastasis.
2. There is a simple staphylococcal fever in which boils are the only obvious lesions (Case 1).
3. Boils are occasionally followed by metastatic abscesses, especially in the lungs, perinephric tissue, heart, and brain (Case 4).
4. Boils may be followed by metastatic lesions, not amounting to abscesses, in the muscles and deep cellular tissues (Case 2).
5. Lung abscess may follow boils (Case 4) or may occur without obvious skin lesions.
6. Deep suppuration in the muscles—pyomyositis—may follow boils (Case 2) or may occur without antecedent skin lesions.
7. Pemphigus contagiosus and other vesicular lesions may be followed by boils.

The cases from the Children's Ward in Singapore were seen in conjunction with Dr. Haridas who kindly supplied statistical information on the incidence of scalp infections in Chinese children.

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## THE HAEMOPOIETIC ACTIVITY OF THE HUMAN STOMACH IN PERNICIOUS ANAEMIA<sup>1</sup>

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### *Introduction*

MODERN views on the aetiology of pernicious anaemia date from the observation of Castle (1929) that when beef was incubated with normal human gastric juice, and the resulting product administered orally to a case of pernicious anaemia, a typical remission and improvement of the blood condition resulted, in all ways similar to that obtained by the feeding of liver. This did not occur when pepsin or the gastric juice of patients suffering from pernicious anaemia was used, and Castle developed the idea of an 'intrinsic factor' of enzymic nature which is distinct from pepsin and is present in the normal stomach, but absent from the stomach in cases of pernicious anaemia.

The relationship between the stomach factor and the active anti-anaemic liver principle has been investigated in these laboratories during the last few years (Wilkinson and Klein, 1932, 1933; Klein and Wilkinson, 1933, 1934) and evidence has been brought forward in support of the view that the liver principle stands in relationship to the stomach factor ('intrinsic factor' or 'haemopoietin') as an end-product of the action of the enzyme on some constituent or constituents of the diet ('extrinsic factor'). Thus, it has been shown that it is possible to prepare *in vitro*, by the action on beef of certain fractions obtained from hog's stomach, an active product which resembles, at any rate superficially, the liver principle, is protein-free and can be administered parenterally as well as orally (Klein and Wilkinson, 1934).

In the present paper, we report further experiments along these lines in which we have been able to show by direct examination of the stomach in pernicious anaemia that haemopoietin ('intrinsic factor') is not present in detectable amount, although present in normal stomachs examined under similar conditions. This finding, of course, was to be expected in view of the extensive investigations that have been carried out in recent years on the constituents of the gastric juice in different conditions. It is now

<sup>1</sup> Received August 6, 1938.

accepted that achylia gastrica is almost invariably a diagnostic feature of pernicious anaemia (Wilkinson, 1932). It may also be found in many other conditions, but not as an invariable finding (Oliver and Wilkinson, 1933).

The presence of haemopoietin in the gastric juice is less easy to demonstrate on account of the large amounts of gastric juice (not readily obtainable in cases of pernicious anaemia) required from the subject, and it has rarely been shown.

### *Experimental*

*Incubation of stomach tissue with beef.* The general procedure used for the preparation of products suitable for injection from human stomachs was as follows: the stomach, freed as far as possible from fat, was finely minced and mixed with  $2\frac{1}{2}$  times its weight of minced lean beef-steak, and  $2\frac{1}{2}$  times its weight of water (the pH then being about 5.5 was not further altered), and the mixture incubated for four hours at 37° C. The product was then heated at 60 to 65° C. for half an hour, cooled and squeezed through muslin. The fluid and washings were treated with two volumes of 90 per cent. alcohol, and after standing overnight, filtered from the copious protein precipitate. The alcoholic filtrate was concentrated *in vacuo* to a small volume (equal to about one-tenth of the water added prior to incubation), and further traces of protein and much salt removed by adding alcohol to a concentration of about 70 per cent. The clear filtrate, after standing overnight, was again concentrated *in vacuo*, until most of the alcohol was removed, and allowed to stand in the ice-chest overnight. The precipitate of salt and fats was filtered off and the filtrate reduced to a thick syrup *in vacuo*. The syrup was allowed to fall slowly with stirring into ten volumes of absolute alcohol and, when the solid had collected at the bottom, the alcohol was changed. The solid precipitate was then removed by filtration and dried in vacuum desiccators. The solid was finely powdered, again dried *in vacuo*, and after solution and sterilization was then ready for use.

*Technique for testing haemopoietic activity.* The test fraction, prepared according to the method described above, was dissolved in a minimum amount of water, sterilized by filtration through a Seitz filter and administered intramuscularly in gradually increasing doses over a period of several days to suitable cases of pernicious anaemia. The effects on the reticulocyte count, the red-cell count, the haemoglobin percentage, and the clinical responses were noted. The patients used were carefully chosen according to the criteria described by us in previous communications (Wilkinson, 1932; Wilkinson and Klein, 1934).

### *Clinical responses to stomach products.*

(a) *The effect of fraction S.I.2 from a beef-normal stomach incubation.* The material used for the preparation of these products was taken from fatal cases following road accidents, or sudden death (cardiac) in otherwise

healthy subjects. Each 100 gm. of fresh stomach tissue yielded 9.8 gm. of fraction S.I.2.

*Test Case PA/419.* A housewife, aged 61 years, was admitted to hospital on June 2, 1934, complaining of weakness, palpitation, dyspnoea, increasing pallor, flatulent dyspepsia, constipation, persistent soreness of the tongue,

TABLE I

*Test Case PA/419. Showing Response to S.I.2, Obtained from Stomach of Normal Subject*

Day.	Reticulocytes per cent.	Red-blood cells per c.mm.	Haemoglobin per cent.	Treatment.
1	1.6	2,450,000	72	Control period. No treatment.
2	1.9			
3	1.3			
4	1.5			
5	1.7			
6	1.9			
7	1.9			
8	1.9	2,460,000	68	
9	1.7			0.5 gm. fraction S.I.2.
10	1.7			1.0 "
11	1.5			2.0 "
12	2.3			3.0 "
13	—			3.0 "
14	4.4			3.0 "
15	4.2	2,320,000	64	3.0 "
16	9.7			3.0 "
17	12.5			3.0 "
18	8.9			3.0 "
19	7.9			3.0 "
20	—			3.0 "
21	8.0			3.0 "
22	3.7	2,720,000	72	Nil
36	1.8	3,520,000	84	Nil
43	1.4	3,720,000	90	30 gm. Pepsac daily.
50	1.0	4,420,000	97	—

some loss of weight, and paraesthesiae in the feet and hands. Examination showed an enlarged spleen and some impairment of reflexes. Among other findings there was achylia gastrica; a negative Wassermann reaction; blood count (2.6.34): red-blood cells, 2,450,000 per c.mm.; haemoglobin, 72 per cent.; colour index, 1.4; white-blood cells, 4,800 per c.mm.; polymorphonuclears, 49.0 per cent.; lymphocytes, 47.0 per cent.; large mononuclears, 3.5 per cent.; eosinophils, 0.5 per cent.; basophils, nil; very marked anisocytosis and poikilocytosis; very few platelets; punctate basophilia and polychromasia noted.

During the preliminary control period the haemoglobin and red cells fell slightly and the patient was then given 33.5 gm. of fraction S.I.2 (equivalent to about 340 gm. normal human stomach) during thirteen days. A good response was obtained, as shown in Table I, the reticulocytes rising to 12.5 per cent. on the ninth day of treatment, which was approximately the expected maximum for the relatively high initial red-cell count. It will be noticed that when the reticulocyte peak had been reached, only 18.5 gm. of the total amount (i.e. 190 gm. stomach) had been administered. There was subsequently a very good response in the red-cell count, haemoglobin value and clinical condition without further treatment.

(b) *Effect of fraction S.I.14 prepared from stomachs of cases of pernicious anaemia.* Fraction S.I.14 was an incubation fraction prepared as above from beef and stomachs taken from two cases of true pernicious anaemia—one untreated and one treated who died from pneumonia during a remission. Each 100 gm. of fresh moist stomach tissue gave 9.1 gm. of fraction S.I.14.

TABLE II

*Test Case PA/540. Showing Failure of Response to Fraction S.I.14 (from Untreated Pernicious Anaemia Stomach) and Subsequent Response to Active Liver Therapy*

Day.	Reticulocytes per cent.	Red-blood cells per c.mm.	Haemoglobin per cent.	Treatment.
1	0.8	1,380,000	28	Control period. No treatment.
2	0.9			
3	—			
4	0.7			
5	0.8	1,280,000	25	0.5 gm. Fraction S.I.14 i.m.
6	—			1.0       "
7	1.4			2.0       "
8	3.0			3.0       "
9	2.0			3.0       "
10	1.5			3.0       "
11	0.8			3.0       "
12	0.5	960,000	23	3.0       "
13	1.8			—
14	—			—
15	1.9	880,000	21	6 c.c. Hepastab i.m.
16	6.2			4       "
17	33.7	1,000,000	22	Nil
18	41.5			Nil
19	54.5			Nil
20	51.7			Nil
21	37.8			Nil
22	20.2			Nil
23	20.1			Nil
26	19.8	2,080,000	40	Nil
30	—			2 c.c. Hepastab.
31	2.3	3,040,000	54	Nil
36	—	3,680,000	64	30 gm. Pepsac daily orally.

*Test Case PA/540.* A housewife, aged 50 years, was admitted to hospital on February 22, 1935, complaining of epigastric pain, nausea, vomiting, flatulence, diarrhoea, loss of energy, weight, and appetite, with shortness of breath and palpitation on exertion. On examination there was severe anaemia, haemic cardiac murmurs, but no enlargement of the liver or spleen. The reflexes were present, but depressed. There was achylia gastrica, a negative Wassermann reaction and a blood count (22.2.35) of: red-blood cells, 1,280,000 per c.mm.; white-blood cells, 3,000 per c.mm.; haemoglobin, 35 per cent.; colour index, 1.35; polymorphonuclears, 50.0 per cent.; lymphocytes, 44.5 per cent.; large mononuclears, 3.5 per cent.; eosinophils, 2.0 per cent.; basophils, nil; marked anisocytosis and poikilocytosis; nucleated red cells, 1 normoblast per 200 white-blood cells; platelets, scanty.

After the preliminary control period she was given 18.5 gm. of fraction S.I.14 (prepared from the stomach of a case of untreated pernicious anaemia) in divided doses intramuscularly—as shown in Table II—without any haematological response, although an excellent result followed the administration of a standard parenteral liver extract.

*Test Case PA/543.* A tram-driver, aged 60 years, complained of extreme weakness, lack of energy, dyspnoea, palpitation, soreness of the tongue, marked loss of weight and appetite, indigestion, flatulence, nausea, vomiting, severe constipation, and paraesthesiae in the limbs and shoulders.

TABLE III

*Test Case PA/543. Showing Lack of Response to S.I.14 (from Treated Pernicious Anaemia Stomach) and Subsequent Response to Active Liver Therapy*

Day.	Reticulocytes per cent.	Red-blood cells per c.mm.	Haemoglobin per cent.	Treatment.
1	0.9	2,040,000	45	Control period. No treatment
2	—			
3	0.8			
4	—			
5	0.7			
6	—			
7	0.8			
8	0.9	1,776,000	46	
9	0.9			—
10	0.9			0.5 gm. Fraction S.I. 14
11	—			1.0 "
12	—			2.0 "
13	1.1			3.0 "
14	1.2			3.0 "
15	1.0	1,650,000	46	3.0 "
16	1.8			3.0 "
17	1.1			3.0 "
18	—			3.0 "
19	1.9			3.0 "
20	1.6			Nil
21	1.6			Nil
22	2.4	1,484,000	42	Nil
23	—			1 gm. L.I. 27
24	3.6			2 "
25	6.4			2 "
26	7.4			Nil
27	7.1			Nil
28	7.6			Nil
29	13.2	1,420,000	44	Nil
30	23.8			Nil
31	28.7			Nil
32	21.0			Nil
33	15.2			Nil
34	12.8			Nil
35	6.5			Nil
36	3.2	2,272,000	61	Nil

Examination showed slight enlargement of the spleen, atrophic glossitis, no impairment of reflexes, achylia gastrica, a negative Wassermann reaction, and a blood count (14.3.35) as follows: red-blood cells, 2,040,000 per c.mm.; haemoglobin, 45 per cent.; colour index, 1.1; white-blood cells, 6,600 per c.mm.; polymorphonuclears, 44.5 per cent.; lymphocytes, 50.0 per cent.; large mononuclears, 3.0 per cent.; eosinophils, 2.5 per cent.; basophils, nil; very marked anisocytosis and poikilocytosis; platelets, scanty.

After the control period, during which the red-cell count fell markedly, he was given 24.5 gm. of fraction S.I.14 (equivalent to 270 gm. fresh stomach), from a treated fatal case of pernicious anaemia in remission,

without any response haematologically. There was, however, a good normal response following the administration of liver fraction L.I.27, as shown in Table III.

Thus it will be noted that the fractions prepared from the incubation mixture of beef and stomachs removed from treated or untreated cases with pernicious anaemia did not possess any haemopoietic activity when tested.

#### Discussion

In previous papers (Wilkinson and Klein, 1933; Klein and Wilkinson, 1934) it has been shown that when stomach fractions containing the thermolabile haemopoietin are incubated *in vitro* with beef muscle, haemopoietically active material is obtained which is relatively thermostable. The substance formed appears from its chemical and therapeutic properties to be similar to the so-called 'anti-pernicious anaemia liver principle', and it can be prepared in a form suitable for injection by methods similar to those used in the case of liver itself. Employing this enzyme reaction, we have found that normal human stomachs, when incubated with beef, yielded haemopoietically active material and consequently contained haemopoietin. On the other hand, stomachs from an untreated case of pernicious anaemia and from a case in complete remission following treatment, but dying from pneumonia, were found to give inactive material; it is therefore inferred that haemopoietin is absent from these stomachs, or at least is present in insufficient amounts to permit of its detection.

These observations are in accordance with the theory already put forward that the enzyme action

Unknown substrate in beef + haemopoietin  $\rightarrow$  active liver principle

which we have demonstrated *in vitro* (Klein and Wilkinson, 1934) also takes place *in vivo* in the normal stomach, but not in the stomach of the patient with pernicious anaemia. The results are in harmony, too, with our previous work on the haemopoietic activity of the human liver (Wilkinson and Klein, 1934), in which it was shown that the normal liver was haemopoietically active, whereas livers from relapsing fatal cases of pernicious anaemia were inactive. On the other hand, we have shown (Wilkinson and Klein, 1934) that in cases of pernicious anaemia in remission, following correct treatment the livers are able to store the anti-pernicious anaemia principle. This is in marked contrast to the stomach which in pernicious anaemia never regains its normal secretory functions. It has been known for a long time that the hydrochloric acid secretion does not return, even though the blood count returns to normal. It has also been shown that the gastric juice does not regain its haemopoietin content. In this communication we have shown further that, whereas the normal stomach contains the anti-anaemic enzyme haemopoietin, stomachs from both treated and untreated cases of pernicious anaemia remain deficient in this respect.

The actual distribution in the stomach of the glands responsible for the

secretion of haemopoietin (intrinsic factor) and their relationship to the known secreting elements of the stomach is not known with certainty; the experiments of Meulengracht (1934) and his co-workers (1934) on the distribution of the haemopoietically active glandular areas in the pig's stomach provide some data on this subject. These authors have carried out clinical tests for haemopoietic activity on preparations of desiccated stomach from the cardiac, fundic, and pyloric portions of the pig's stomach. The results with preparations from the pylorus were haemopoietically very active, while those from the cardiac region showed negative or doubtful activity, and those from the fundus were quite inactive. It is of interest that the amounts of pepsin and rennin in these three preparations followed the inverse order, being small in the pyloric region, but considerable in the fundic preparations. Further, Meulengracht has suggested that the Brunner's glands in the duodenum have a similar function to the pyloric glands in producing haemopoietin. As a result of these observations, and in view of the histological resemblance of the pig's stomach to the human stomach, it was suggested that pernicious anaemia in man is due principally to atrophy and consequent inactivity of the pyloric and Brunner's glands. Thus, *prima facie*, atrophy of the remaining portions of the stomach (with consequent achylia gastrica) should not be essential in pernicious anaemia. In 1937, however, Meulengracht found from an examination of stomachs obtained *post mortem* from cases of pernicious anaemia, that there was a severe atrophy of the fundic region with intestinal heterotopia, although there were no alterations in the pylorus or duodenum. Similar observations by Magnus and Ungley (1938) appear to confirm these observations, which differ from the views that have so far been held.

It has also been shown that haemopoietic activity exists in other parts of the gastro-intestinal tract; thus, active preparations were made from duodenum by Sharp, McKean, and Heide (1931), Gutzeit (1932), Meulengracht (1935, 1936), Uotila (1936), Thompson (1937), but not by Henning and Brugsch (1931); Schemensky (1935) claimed to have detected some anti-anaemic activity in dried colon. Uotila (1938) considers that the duodenum and ileum contain as much, if not more, anti-anaemic potency than the stomach apart from the pylorus, while the ileum appears to be the greatest reservoir. From the results claimed by these various authors, anti-anaemic potency of the gastro-intestinal tract may be present in the following order of descending potency—pylorus, ileum, duodenum, jejunum, cardia, colon, fundus. If these observations are correct, then other possibilities arise and the part played by the Brunner's and pyloric glands may not, as anticipated, be so specific in this respect, while the difficulty of explaining the relatively rare occurrence of pernicious anaemia after gastrectomy becomes easier. Morrison (1936) believes that the oxyntic cells of the stomach produce the intrinsic factor, while a further suggestion by Erös and Kunos (1936) would implicate the argentaffine system of the gastro-intestinal tract, since these authors found complete atrophy of the argentaffine cells in cases

of pernicious anaemia, but their evidence is not very convincing. Nevertheless, the almost invariable association of achylia gastrica with true pernicious anaemia cannot be ignored and is an established diagnostic feature of some significance which has been discussed elsewhere (Wilkinson, 1932; Oliver and Wilkinson, 1933). It is difficult, if not impossible, to dissociate its occurrence from the other changes in the gastro-intestinal tract in pernicious anaemia, but clearly much more investigation is required.

#### Summary

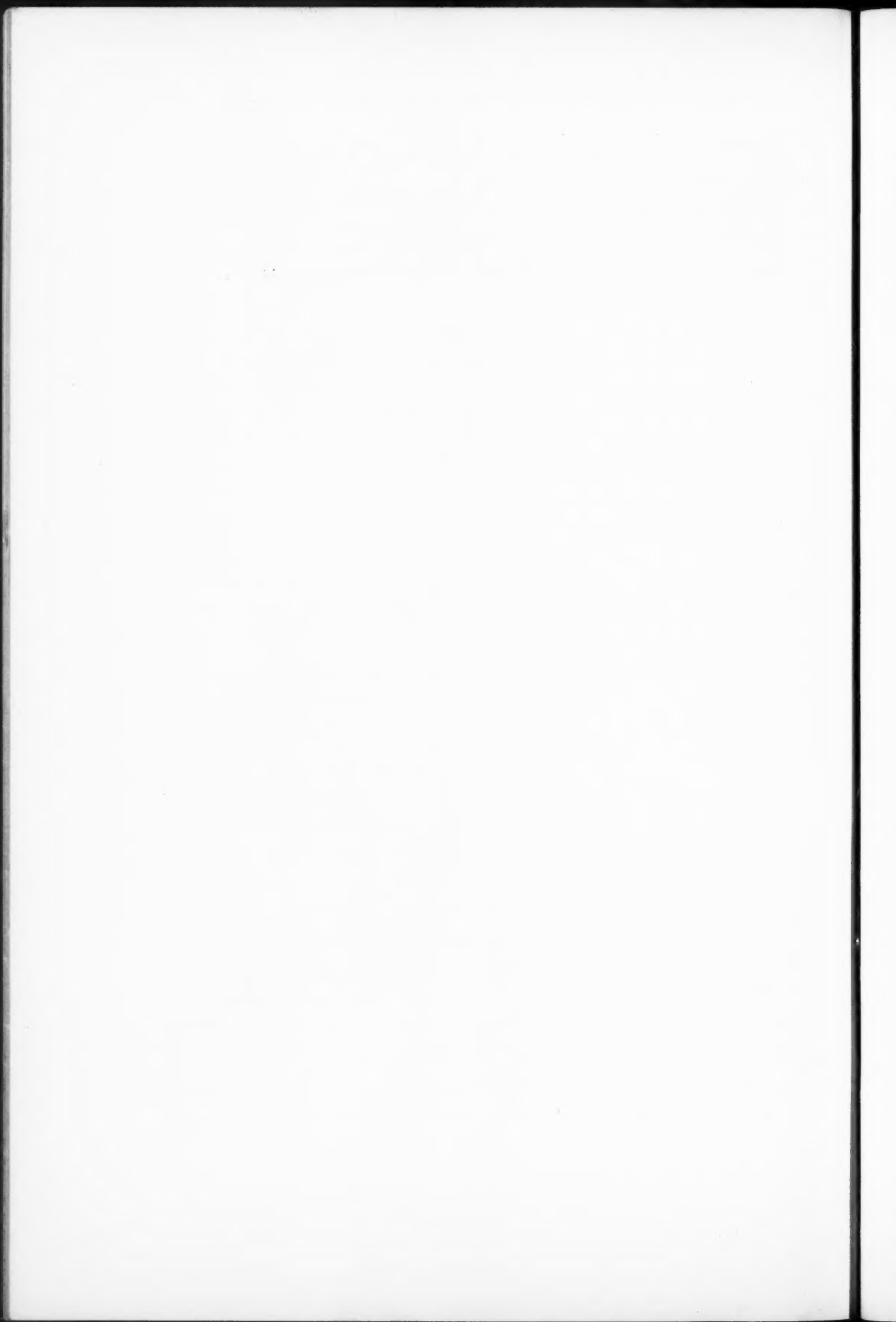
The fraction resulting from the treatment of the incubation mixture of normal human stomachs with beef muscle, by methods analogous to those used in the case of parenteral preparations from liver, was found to be haemopoietically active in the treatment of pernicious anaemia. On the other hand, stomachs from fatal cases, relapsing cases, or cases in remission of pernicious anaemia yielded haemopoietically inactive fractions under the same conditions. It is, therefore, inferred that the enzyme haemopoietin, which is already known to be present in the stomachs of the hog, the silver fox, and many other animals, is also present in normal human stomachs, but is absent from or is present in too small amounts to be detected, in the stomachs of subjects suffering from pernicious anaemia, whether untreated or in remission following adequate treatment. The significance of these results is considered.

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## AN INVESTIGATION INTO THE TREATMENT OF PARKINSONISM WITH BULGARIAN BELLADONNA<sup>1</sup>

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With Plate 32

VARIOUS preparations of stramonium and belladonna and their alkaloids have been used in the treatment of the Parkinsonian state since the latter became widespread in the years following the war. Although there has been no unanimous opinion as to which drug was preferable, the general consensus has been that there was no great difference between the various preparations of each drug.

In 1935 Panegrossi reported on a method which had been advocated for some time by Ivan Raef of Bulgaria. Panegrossi stated that by using extracts from plants of the belladonna group grown in Bulgaria, the results were better than with any other of the drugs in use. Emphasis was laid on the fact that not only did this method of treatment lead to greater improvement, but also that the improvement was maintained at least for a time after the drug was stopped. This and other favourable reports by Italian workers led to the widespread adoption of this method throughout Italy. Other continental writers, Marinesco and Façon (1936), Soldi and Trabucchi (1936), and others, were unable to confirm this difference between the effect of extracts of plants grown in Bulgaria and those grown elsewhere.

It was not reported on in England until 1937, when Neuwahl and Fenwick described their experience with two cases treated with Bulgarian belladonna, and expressed their opinion that greater and more permanent improvement could be obtained by this means than by any other method at present in use. In their paper they compare the effect obtained by giving 15 c.c. of the decoction of Bulgarian belladonna to a patient in an institution with the effect of giving 20 minims of the B.P. tincture of belladonna to the same patient in his house.

It was felt that in order to gauge accurately the effect of the Bulgarian belladonna, it was essential that equivalent doses of the drugs in question should be used, and that they should be controlled by graphic methods and not left to the subjective impressions of the observer and patient. This we have endeavoured to do, attention being paid in this study to the effect of the various drugs of the belladonna group. Raef, in instituting the Bulgarian treatment, advised that certain powders and pills be taken as well as the decoction of belladonna. As these powders and pills consist of

<sup>1</sup> Received August 6, 1938.

pharmacological preparations which have been shown by Di Mattei (1935) to have no therapeutic value in this condition, it was decided that the belladonna root was the essential part of the treatment, and that part worth investigating. The comparative effects of four groups of drugs were investigated.

1. *Decoction of Bulgarian root of belladonna.* This was prepared in the manner described by Neuwahl and Fenwick (1937) by British Drug Houses, Ltd. From this firm we received the information that although the method did not give a very exact or constant amount of the essential principles, the approximate strength of the decoction was two-thirds the strength of the B.P. tincture of belladonna.

2. *English belladonna.* This was used in two preparations: (a) the B.P. tincture, and (b) a decoction made in a similar way to that used in the making of the decoction of the Bulgarian root.

3. *Stramonium.* Three preparations were used: (a) the B.P. tincture (1932); (b) the Extractum Stramonium Siccum, U.S.P., and (c) a decoction of Bulgarian root. The strength of these preparations was as follows: 0.25 gm. of the dry extract of stramonium equalled six drachms of the tincture of stramonium B.P. (1932), and the strength of the decoction was half that of the B.P. tincture of stramonium.

4. *Trasentin.* This is a synthetic proprietary preparation (Ciba Ltd.) which is claimed to have an antispasmodic effect similar to that of atropine, but without unpleasant side effects on the pupil, heart, or salivary glands. It is said to act not only on the neural mechanism, as atropine does, but also directly on the musculature as papaverine does.

#### Methods

These investigations were all carried out on patients admitted to the hospital. The Bulgarian decoction was given according to the method described by Neuwahl and Fenwick. It was first given once daily in a small dose last thing at night. The dose was gradually increased, and when a moderate-sized dose was reached, it was divided and given twice a day. A clear week or more without medication was arranged between giving stramonium and Bulgarian belladonna to ensure that the patients had returned to their original untreated state. In two cases, the Bulgarian belladonna was given first, in one case stramonium was given first, and in two cases stramonium was given both before and after the Bulgarian belladonna. Owing, however, to the time necessary for working up to the full doses of belladonna, it was not always found practicable to allow a period between the administration of Bulgarian and English belladonna, so patients were transferred directly from one to the other.

In order that an objective comparison between the effect of the various treatments could be made, graphic records were taken from the patients at all stages of treatment. This was done by means of a modified ergograph,

and the patients were instructed to flex and extend at the elbow as rapidly as possible, the movements being recorded on a smoked drum; thus both the rate and extent of rapidly alternating movements at the elbow could be estimated. In analysing the records, the rate and extent of movement were both taken into consideration and also the figure representing the product of the two measurements. Patients seemed to vary individually as to whether improvement occurred in the rate of movement or in the excursion of the movement, consequently it was felt that the product of the two factors was as good an indication of their altered state as could be obtained from the records.

No satisfactory method was available for recording the variation in tremor, as none could take into account the fact that emotional disturbances altered the tremor. Only a broad impression based on observation of the effect on tremor could be gained. Notes were also made of the patient's own impressions, but it was found that these were quite unreliable, as the patients tended to judge the efficacy of any treatment by the degree of unpleasantness of the side effects of the drug.

#### *Cases*

Five patients were investigated.

*Case 1.* C. D. (male) aged 41 years. Admitted 27.8.37 under Dr. Hinds Howell. Onset of symptoms occurred three years earlier following 'influenza'. He had well-marked Parkinsonian facies and gait, with coarse tremor of all four limbs, more marked on the right side. He was able to dress and feed himself.

*Case 2.* R. S. (female) aged 36 years. Admitted 20.10.37 under Dr. Grainger Stewart. Eleven years before while pregnant, she had an attack of drowsiness, diplopia, and difficulty in sleeping at night. Symptoms of Parkinsonism began five years before, slowly progressed and on admission were well-marked. She was able to feed herself, but not to use a knife, and to dress and undress very slowly. Speech was particularly affected.

*Case 3.* E. W. (female) aged 47 years. Admitted 1.11.37 under Dr. E. A. Carmichael. She had 'influenza' in 1924 in Australia with no neurological symptoms. Present symptoms began four years before and steadily progressed. She was in an advanced Parkinsonian state and had been bed-ridden for 12 months. She was unable to dress herself or cut up her food, but could feed herself with mashed food. She was particularly troubled with salivation.

*Case 4.* R. S. (male) aged 46 years. Admitted 24.2.38 under Dr. Grainger Stewart. He had 'influenza' in 1931 with headache and drowsiness for a week. Present symptoms began two years ago. He had typical Parkinsonism of moderate severity, with slowness of movement and tremor, particularly down the right side. He was able to dress and feed himself.

*Case 5.* C. F. (male) aged 57 years. Admitted 1.3.38 under Dr. E. A. Carmichael. There was a very gradual onset of symptoms 12 years before. He was a moderately advanced case of paralysis agitans, with marked tremor and some rigidity, especially down the right side. He was able to dress and feed himself, but was much troubled by the tremor.

*The effect of decoction of Bulgarian belladonna.* All five cases were treated with this preparation. The initial dosage was 2 c.c. and was increased to

a maximum of 20 to 26 c.c. twice daily. Considerable side effects were produced: dryness of the mouth became troublesome when the dose reached 8 to 10 c.c. twice daily, and at slightly over this level, paralysis of accommo-

TABLE I

*Case 1. C. D., Male Aged 41 Years. Admitted 27.8.37. Records from R. Arm with Weight*

Date.	Treatment.	Rate per 20 secs.		Excursion in cm.		Product.		Length of record in secs.
		B.	E.	B.	E.	B.	E.	
28.8.37	Tr. Stramon. $\eta$ 30 t.i.d.							
2.9.37	" $\eta$ 30 q.i.d.							
4.9.37	" $\eta$ 60 t.i.d.							
8.9.37	" $\eta$ 60, Hyoscine							
	Hbr.gr. 1/150 t.i.d.							
10.9.37	Massage and exercises							
12.9.37	Mist. q.i.d.							
17.9.37	Tr. Stramon. $\eta$ 70, Hyos. HBr.							
	1/120 q.i.d.							
23.9.37	Tr. Stram. $\eta$ 70, Hyos. Hbr.							
	1/100							
14.10.37	Tr. Stram. $\eta$ 70, Hyos. Hbr.	22½	18	6.31	6.11	141.1	109.9	187
	1/100							
15.10.37	None							
19.10.37	"	17	15	7.07	5.45	112.0	81.8	205
21.10.37	"	18	17	6.26	3.95	111.3	67.1	191
21.10.37	Bulgarian bellad. 5 c.c. nocte							
22.10.37	Bulgarian bellad. 8 c.c. nocte							
23.10.37	" 10 "							
24.10.37	" 12 "							
25.10.37	" 14 "							
27.10.37	" 10 c.c. b.d.							
29.10.37	" 12 "							
31.10.37	" 14 "							
2.11.37	" 10 "							
6.11.37	" 12 "							
8.11.37	" 14 "							
9.11.37	" 16 "	18½	16½	7.56	5.53	145.0	92.9	195
11.11.37	" 18 "							
12.11.37	" 20 "							
15.11.37	" 20 "	20	20	5.70	5.20	114	104	216
17.11.37	None							
23.11.37	"	17	17	5.36	3.64	91.1	60.8	196
23.11.37	Trasentin 1 tablet							
25.11.37	" 2 tablets t.i.d.							
29.11.37	" 2 "	19	14½	6.64	4.49	126.2	65.0	178
31.11.37	Bulgarian bellad. 8 c.c. b.d.							
6.12.37	" " "	20	19	7.1	5.71	142.0	108	167
9.12.37	Tr. Bellad. B.P. 5 c.c. b.d.							
16.12.37	" " "	20½	19	7.08	6.07	149.6	115.3	—
	(Discharged on this 17.12.37)							
9.5.38	Tr. Bellad. B.P. 5 c.c. b.d. (As out-patient)	17½	17	6.73	5.23	117.8	88.9	193

B = beginning.

E = end.

dation set in, coming on at first for an hour or two after the dose, later being permanent during the administration of the drug. The dryness of the mouth was found to interfere with meals in some cases, but by adjusting the time of the dose and giving milk half-an-hour later, this was rendered

## AN INVESTIGATION INTO TREATMENT OF PARKINSONISM 569

tolerable. Eserine drops to the eyes were given in two cases with some relief of the difficulty in reading. In one case (Case 1) there was a suggestion of delirium with the higher dose, but this did not go beyond a mild restlessness

TABLE II

Case 2. *R. S., Female Aged 36 Years. Admitted 20.10.37. Records taken with Weight from L. Arm*

Date.	Treatment.	Rate per 20 secs.		Excursion in cm.		Product.		Length of record in secs.
		B.	E.	B.	E.	B.	E.	
22.10.37	None	10	—	4.24	—	42.4	—	All movement ceased after 164 secs.
26.10.37	Bulgarian bellad. 5 c.c. nocte							
28.10.37	" 7 "							
29.10.37	" 8 "							
31.10.37	" 10 "							
1.11.37	" 12 "							All movement ceased after 164 secs.
3.11.37	" 8 c.c. b.d.							
5.11.37	" 10 "							
6.11.37	" 12 "							
7.11.37	" 14 "							
8.11.37	" 16 "	14½	18	5.04	3.38	73.0	60.8	185
10.10.37	" 18 "							
11.11.37	" 20 "							
12.11.37	" 22 "							
14.11.37	" 24 "							
15.11.37	" 24 "	13½	17½	5.21	3.26	70.4	57.05	199
23.11.37	" 26 "							
23.11.37	" 26 "	15½	19½	4.71	3.03	74.2	59.1	190
30.11.37	" 26 "							
1.12.37	" 26 "	17½	20	4.78	3.03	83.6	60.6	161
2.12.37	Tr. Bellad. B.P. 18.25 c.c. b.d.							
7.12.37	" " "	18	20	5.27	3.10	94.9	62.0	182
16.12.37	" " "	21	24	4.67	2.59	98.07	62.16	199
29.12.37	Mist. Gent Alk. t.i.d.							
3.1.38	None							
4.1.38	"	17	16	3.52	2.59	57.34	41.44	171
6.1.38	Trasentin 3 tablets t.i.d.							
7.1.38	" 4 "							
8.1.38	" 5 "							
13.1.38	" 5 "	20	20	4.41	2.35	88.0	47.0	—
14.1.38	None							
18.1.38	"	19	18½	3.15	2.02	59.85	37.37	—
19.1.38	Ext. Stramon. Sicc. gm. 0.25 b.d.							
20.1.38	" " gm. 0.25 t.i.d.							
27.1.38	" " " "	16	18	6.64	4.16	106.24	75.28	—

B = beginning. E = end.

and loquaciousness. There was in two cases some rise in pulse-rate, but in only one of these did the rate exceed 120 per minute. In this case (Case 4) the pulse-rate was habitually fast and frequently rose to 110 for no apparent reason. In the other three cases there was no significant rise of the pulse-rate. In one case (Case 4) the drug gave rise to fairly severe parasthesiae in the arms and legs, particularly after the evening dose. These were likened to a 'burning fire' and kept the subject awake for an hour or two. On the whole, therefore, the patients stood these large doses of the Bulgarian decoction remarkably well.

*Effect on voluntary movement.* In all the cases large doses of Bulgarian decoction were of undoubted benefit and the patients moved more freely and the records showed considerable improvement. It was noted, however,

TABLE III

*Case 3. E. W., Female Aged 47 Years. Admitted 1.11.37. Records taken with Spring.*

Date.	Treatment.	Rate per 20 secs.		Excursion in cm.		Product.		Length of record in secs.
		B.	E.	B.	E.	B.	E.	
4.11.37	None	8	6 $\frac{3}{4}$	2.52	1.95	20.16	13.15	184
		9 $\frac{1}{2}$	9	2.12	1.59	20.65	14.13	182
4.11.37	Bulgarian bellad. 6 c.c. nocte							
6.11.37	" 8 "							
8.11.37	" 10 "							
9.11.37	" 8 c.c. b.d.							
10.11.37	" 10 "							
12.11.37	" 12 "							
15.11.37	" 12 "	14	10 $\frac{1}{2}$	2.75	2.17	38.5	22.8	191
		14 $\frac{1}{2}$	12	2.82	1.92	40.8	23.04	185
16.11.37	" 15 "							
20.11.37	" 18 "							
22.11.37	" 20 "							
23.11.37	" 20 "	18	14 $\frac{1}{2}$	3.31	1.54	59.6	22.35	184
		20 $\frac{1}{2}$	19	3.35	2.39	68.6	45.4	177
1.12.37	" 20 "	17	16	3.1	1.7	52.7	26.2	179
		17	15	3.50	2.61	59.5	39.3	170
2.12.37	Tr. Bellad. B.P. 12.5 c.c. b.d.							
8.12.37	" " "	20	20	2.75	1.23	55.0	24.6	187
		20	20	3.5	1.64	70.0	33.2	188
17.12.37	" " "	28	24	3.0	0.55	84.0	16.5	—
		24	22	3.3	1.58	79.2	34.8	—
29.12.37	None							
6.1.38	"	23	—	1.29	—	29.67	—	Movement ceased after 101 secs.
		21	16	2.51	0.45	52.71	7.2	
6.1.38	Trasentin 3 tablets t.i.d.							
7.1.38	" 4 "							
8.1.38	" 5 "							
11.1.38	" 5 "							
13.1.38	" 5 "	20	16	2.09	0.56	41.8	8.86	—
		23	20	2.3	0.78	52.9	15.6	—
14.1.38	None							
18.1.38	"	21	18	1.52	0.3	31.92	5.4	—
		20	18 $\frac{1}{2}$	1.92	0.4	38.4	7.7	—
19.1.38	Ext. Stramon. Sicc. gm. 0.25 b.d.							
20.1.38	" " gm. 0.25 t.i.d.							
21.1.38	" " gm. 0.25 b.d.							
27.1.38	" " gm. 0.25 b.d.	20	20	2.34	0.95	46.8	19.0	—
		27	26	2.53	0.76	68.31	19.76	—

B = beginning. E = end. Right arm—roman. Left arm—italic.

from the records, that the maximum improvement was not in every case associated with the largest dose given. In one case (Case 3) the maximum improvement was obtained with the largest dose given—namely, 20 c.c. twice daily (see record taken on 23.11.37). This patient was the most advanced case of the series and stood the large dose with very little disturbance beyond paralysis of accommodation. In the other four cases doses

# AN INVESTIGATION INTO TREATMENT OF PARKINSONISM 571

ranging from 10 c.c. to 14 c.c. twice daily were found to be as efficient or more efficient than the larger doses. Thus in Case 1 comparison of the record taken 9.11.37, when he was on 14 c.c. twice daily with that taken

TABLE IV

Case 4. R. S., Male Aged 46 Years. Admitted 24.2.38. Records from R. Arm. New Spring.

Date.	Treatment.	Rate per 20 secs.		Excursion in cm.		Product.		Length of record in secs.
		B.	E.	B.	E.	B.	E.	
2.3.38	None	8	4	2.0	1.61	16.0	6.44	290
2.3.38	Ext. Stramon. Sicc. gm. 0.25 b.d.							
8.3.38	" " gm. 0.25 t.i.d.							
9.3.38	" " "	17	17	4.01	3.93	68.17	66.81	197
15.3.38	" " "	18	11	3.48	2.89	62.64	31.79	207
16.3.38	" " " q.i.d.							
22.3.38	" " "	11	10	3.6	3.59	39.6	35.9	186
25.3.38	Mist. Gent. Alk. " t.i.d.							
29.3.38	" " "	10½	5	2.15	1.96	22.6	9.8	188
30.3.38	Bulgarian bellad. 3 c.c. daily							
31.3.38	" 4 "							
1.4.38	" 6 "							
2.4.38	" 8 "							
5.4.38	" 8 "	14	8	2.84	2.52	39.75	20.16	205
6.4.38	" 12 "							
8.4.38	" 8 c.c. b.d.							
9.4.38	" 10 "							
11.4.38	" 12 "							
12.4.38	" 14 "	17	11	2.74	2.64	46.6	29.0	199
14.4.38	" 16 "							
16.4.38	" 18 "							
17.4.38	" 18 c.c. a.m.							
17.4.38	None p.m.							
18.4.38	" "							
19.4.38	" a.m. Bulgarian bellad. 18 c.c. p.m.							
20.4.38	18 c.c. a.m. 12 c.c. p.m.	14	10½	2.73	2.11	38.22	22.2	199
21.4.38	Bulgarian bellad. 14 c.c. b.d.							
22.4.38	" 18 "							
23.4.38	" 18 "	16	10½	2.68	2.69	42.0	28.0	199
25.4.38	" 18 "							
26.4.38	" 20 c.c. a.m.	14	9	2.81	2.16	39.34	19.44	208
26.4.38	" 10 c.c. p.m. thereafter b.d.							
28.4.38	Decoction bellad. B.P. 10 c.c. b.d.							
3.5.38	" " 10 c.c. a.m.	15½	10½	3.53	3.12	54.7	32.8	182
3.5.38	Decoction stramonium 7 c.c. nocte							
4.5.38	Decoction stramonium 7 c.c. b.d.							
5.5.38	" " 8 "							
6.5.38	" " 8 "	14	9½	2.86	2.5	40.0	23.75	181
7.5.38	" " 10 "							
9.5.38	" " 12 "							
10.5.38	" " 12 "	15½	12	3.12	3.19	48.0	38.0	182

B = beginning. E = end.

15.11.37, when he was on 20 c.c. twice daily, shows that, although the rate has increased slightly, the excursion has fallen off considerably. Also in Case 2,

TABLE V

Case 5. C. F., Male Aged 57 Years. Admitted 1.3.38. Record from L. Arm. New Spring.

Date.	Treatment.	Rate per 20 secs.		Excursion in cm.		Product.		Length of record in secs.
		B.	E.	B.	E.	B.	E.	
1.3.38	None							
3.3.38	Massage and exercises	24	18	3.07	1.14	73.68	20.52	193
9.3.38	" "							
9.3.38	" "	15	19	2.73	1.83	40.95	24.77	191
15.3.38	" "							
15.3.38	Ext. Stramon. Sicc. gm. 0.25 b.d.	20	17	3.09	1.13	61.8	19.21	202
16.3.38	Stopped							
17.3.38	Ext. Stramon. Sicc. gm. 0.06 b.d.							
20.3.38	" " gm 0.25 "							
22.3.38	" " " "	23	21	2.87	2.68	66.0	56.28	203
25.3.38	" " " t.i.d.							
29.3.38	" " " "	20	20	2.72	1.83	54.4	36.6	202
30.3.38	None							
2.4.38	Bulgarian bellad. 3 c.c. nocte							
3.4.38	" 4 "							
4.4.38	" 6 "							
5.4.38	" 6 "	20	20	2.46	1.27	49.2	25.4	200
6.4.38	" 10 "							
7.4.38	" 12 "							
9.4.38	" 8 c.c. b.d.							
10.4.38	" 10 "							
12.4.38	" 12 "	22	20	2.97	0.85	65.3	17.0	211
14.4.38	" 14 "							
16.4.38	" 16 "							
17.4.38	" 16 c.c. a.m. none p.m.							
18.4.38	None							
19.4.38	" a.m. Bulgarian bellad. 18 c.c. p.m.							
20.4.38	Bulgarian bellad. 18 c.c. a.m. 16 c.c. p.m.							
20.4.38		22	21	3.55	2.2	78.1	46.2	119
21.4.38	Bulgarian bellad. 18 c.c. b.d.							
23.4.38		21	22	2.47	2.25	51.87	49.5	182
24.4.38	Bulgarian bellad. 22 c.c. b.d.							
25.4.38	" 24 "							
26.4.38	" 24 c.c. a.m.	21	25	2.75	2.29	57.75	57.25	196
26.4.38	" 10 c.c. b.d.							
28.4.38	Decoction bellad. B.P. 10 c.c. b.d.							
3.5.38	" 10 "	23½	26½	2.9	2.13	68.15	56.4	185
3.5.38	Decoction stramon. 7 c.c. p.m.							
4.5.38	" 7 c.c. b.d.							
5.5.38	" 8 "							
6.5.38	" 8 "	20	25	3.65	2.5	73.0	62.0	181
9.5.38	" 9 "							
10.5.38	" 10 "	25½	28	3.47	2.05	90.7	56.0	190

B = beginning. E = end.

where the same relation is seen between the record taken 8.11.37 and that taken 1.12.37, when the doses were 14 c.c. and 26 c.c. twice daily respectively. In Case 5 the record taken on 3.5.38 on 10 c.c. twice daily showed no appreciable difference from that taken on 26.4.38, when the dosage was 24 c.c. twice daily. It was at this level of dosage—10 to 14 c.c. twice

daily—that the side effects of the drug began to be unpleasant. The impression was gained that the optimum dose was one which gave rise to moderate, but not extreme, signs of intolerance. These doses were equivalent to 125 to 180 minims of the B.P. tincture of belladonna.

The claim has been made (Panegrossi, 1935 *a*) that treatment with Bulgarian belladonna has an effect which is more or less permanent. This could not be confirmed in our series of cases. Thus in Case 1 comparison of the records 19.10.37 and 23.11.37, each taken when the patient was receiving no treatment, show that there was no lasting improvement after a full course of Bulgarian belladonna.

*Comparison with other drugs. English belladonna.* This was employed in two forms, the tincture and a decoction. Three cases (Cases 1, 2, and 3) were transferred directly from the decoction of Bulgarian belladonna to the B.P. tincture of belladonna in equivalent doses. There was no noticeable alteration in the side effects produced, which confirmed the impression that the doses contained equivalent amounts of the active principles. The comparison of the records taken in Case 1 on 6.12.37 and 16.12.37, in Case 2 on 1.12.37 and 17.12.37, show that there was no appreciable difference in the results obtained with the Bulgarian and the English drug. Cases 4 and 5 were transferred directly from the decoction of Bulgarian belladonna to the decoction of English belladonna. In these two cases a smaller dose of the English belladonna was given, as the side effects of the Bulgarian belladonna were becoming unpleasant. In neither case was the patient aware of the change of drug, and comparison of the records taken 26.4.38 and 3.5.38 from both cases shows that the results with Bulgarian belladonna were no better than those with English belladonna.

*Stramonium.* Three preparations of stramonium were used, the tincture, the dried extract (U.S.P.) and a decoction. The tincture was given in one case (Case 1). This patient had been admitted before the investigation began and was having three times a day a mixture of tincture of stramonium 70 minims and hyoscyne hydrobromide 1/100 grain. He stood this dose with no obvious side effects and his record on this medication was as good as on the largest dose of belladonna, either English or Bulgarian. The dried extract was given in doses of 0.25 gm. three or four times a day. Cases 2 and 4 stood this dosage three times a day well and were considerably better on this preparation than on any of the belladonna preparations. Their records, 27.1.38 in Case 2, and 9.3.38 in Case 4, show a degree of improvement not reached with any of the other drugs. Cases 3 and 5 did not stand this large dosage very well and both developed slight signs of delirium; and the records taken in Case 3, on 27.1.38, and in Case 5 on 22.3.38, and on 29.3.38, were not so good as the best during the belladonna medication. In Case 3 there was unfortunately no opportunity of trying any other preparation of stramonium; Case 5 was later put on to a decoction of stramonium and this, which was well tolerated, gave better results than the belladonna (record of 10.5.38). Case 4 was also given the decoction of

stramonium in doses up to 12 c.c. twice a day (equivalent to 6 c.c. of the B.P. tincture of stramonium). This gave a result equal to that obtained with either of the belladonna preparations, but not so good as that obtained with the equivalently larger doses of the dried extract of stramonium.

Thus to summarize the effect of the various preparations of stramonium: five cases were given belladonna and stramonium; three were better on stramonium, one was equally improved by both, and in one the belladonna was better than the stramonium. One patient (Case 5) volunteered the statement that the decoction of stramonium was the only preparation that really helped his tremor.

*Trasentin.* This was given to Cases 1, 2, and 3. In Case 1, two tablets three times daily, and in Cases 2 and 3, five tablets thrice daily were given. In Case 3 trasentin led to a slight improvement in salivation; in the others there was no subjective change, and although some of the records show a slight improvement, this is negligible when compared with that obtained with the other drugs.

#### Summary

1. The comparative effect of Bulgarian belladonna root, English belladonna root, and stramonium was studied in five cases of Parkinsonism by means of graphic methods.

2. In these cases there did not appear to be any advantage in using the Bulgarian belladonna in preference to the English belladonna, nor was there any appreciable difference between belladonna given as a decoction and belladonna given as the standard B.P. tincture.

3. In four of the cases, preparations of stramonium were more, or equally as effective as preparations of belladonna. In one case belladonna seemed to be better than stramonium.

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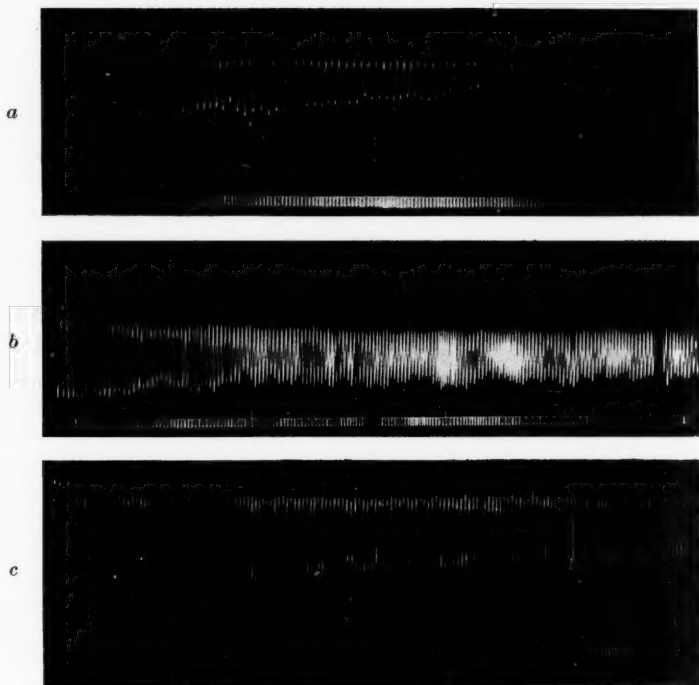


Fig. 1. Case 2. Records each of about three minutes' duration.

a. On admission. b. On Bulgarian belladonna 26 c.c. b.d.  
c. On extractum stramonium siccum 0.25 gm. t.i.d.

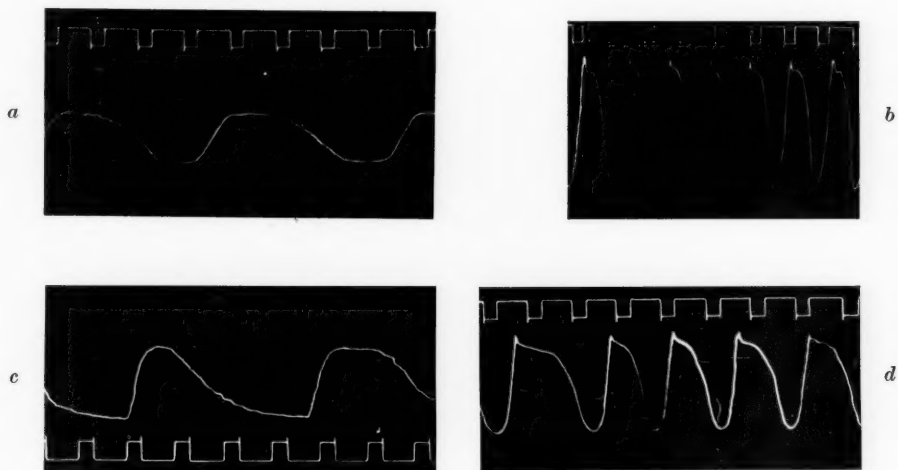
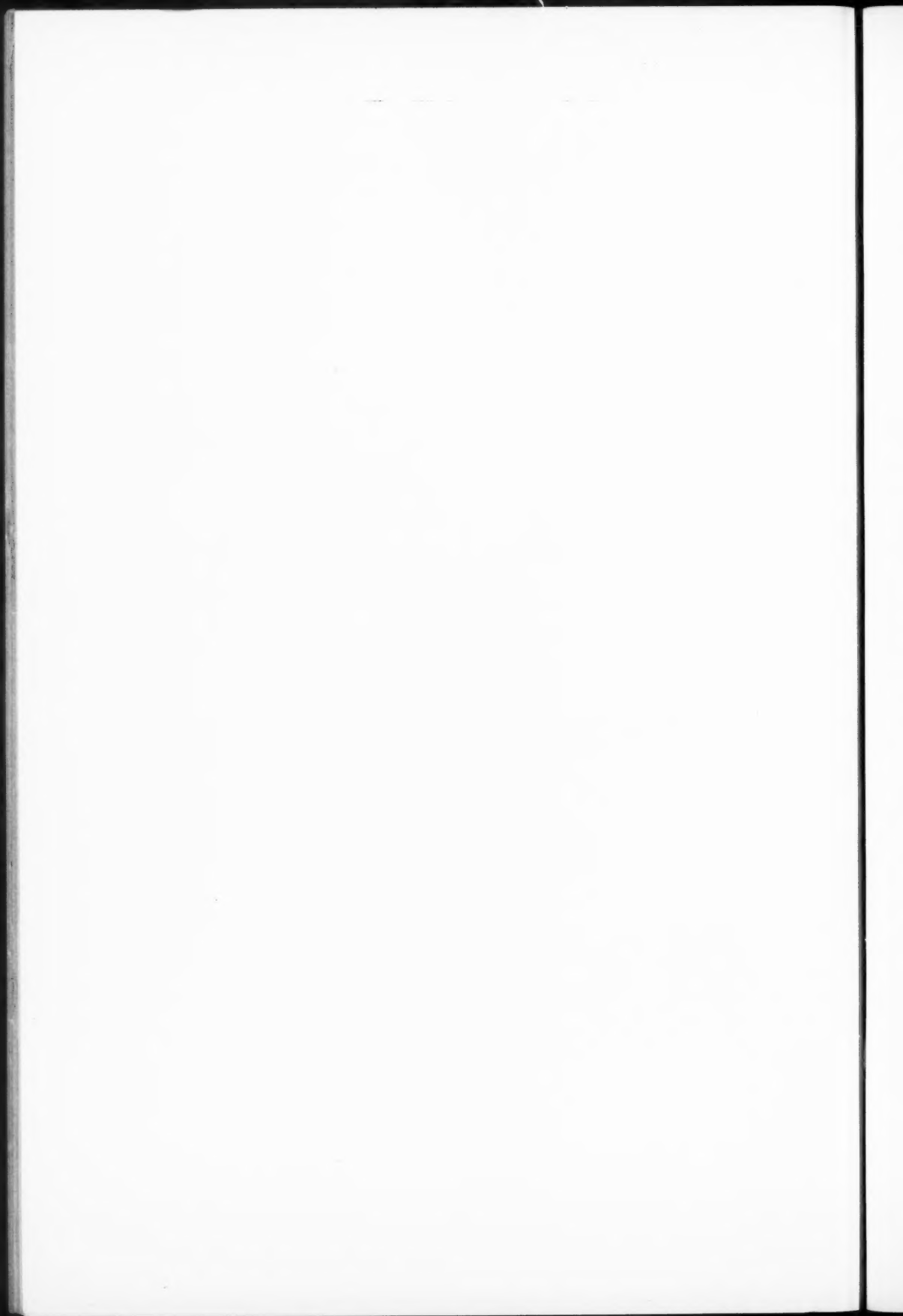


Fig. 2. Case 4. Records at a faster rate, each of eight seconds' duration, showing the rate and excursion of movement.

a. On admission. b. After taking stramonium for seven days. c. After all treatment was suspended for five days. d. After Bulgarian belladonna for twenty-four days.



## OBSERVATIONS ON THE RELATION OF LEUCOCYTOSIS TO ASCORBIC ACID REQUIREMENTS<sup>1</sup>

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### *Introduction*

NUMEROUS methods have been described for the estimation of vitamin C, but the one which is now most widely used is that described by Harris and his co-workers. Their method is a quantitative modification of Tillmans' technique (Tillmans, 1930; Tillmans, Hirsch, and Vaubel, 1933), using the reagent 2, 6, dichlorophenol indophenol (Harris, Ray, and Ward, 1933; Harris and Ray, 1935). The simplicity of this chemical method, when compared with the pre-existing technique of biological assay, has led to an abundance of investigation in this field. It has been known for many years that scurvy is due to a lack of vitamin C, but recently suggestions have been made that deficiency of this factor is associated with many other conditions. In fact, so many papers have now been published on this subject that it is difficult to find a single ailment to which the human or animal body is prone that has not been investigated from this point of view. Reports have claimed a therapeutic action for ascorbic acid in every condition from congestive heart failure (Evans, 1938) to diabetes mellitus (Pfleger and Scholl, 1937). This plethora of chemical research gave rise to a conception of vitamin C requirements which probably bore little relation to the biological needs in health. Thus such terms as 'sub-scurvy state' (Archer and Graham, 1936), 'conditioned scurvy' (Engelkes, 1935), 'vitamin C subnormality' (Harris, Abbasy, Yudkin, and Kelly, 1936), and 'asymptomatic scurvy' (Ingalls and Warren, 1937) occur with an increasing frequency in the literature. While admitting that the standards may be artificial, we may agree that during the course of acute and chronic infections, a lowered level of nutrition for vitamin C usually occurs. This deficiency may be judged by the following criteria, which for the sake of comparison have been numbered separately, but the first three criteria should be considered as steps in a single test (Harris and Ray, 1935).

1. An increased requirement of vitamin C to maintain the 'minimal standard' excretion of ascorbic acid in the urine (Harris, Abbasy, Yudkin, and Kelly, 1936; Abbasy, Hill, and Harris, 1936; Abbasy, Harris, and Hill, 1937; Abbasy, Harris, and Ellman, 1937; Jetter and Bumbalo, 1938).

<sup>1</sup> Received July 25, 1938.

2. A diminished urinary response to test doses of ascorbic acid (Harris, Abbasy, Yudkin, and Kelly, 1936; Abbasy, Hill, and Harris, 1936; Abbasy, Harris, and Hill, 1937; Abbasy, Harris, and Ellman, 1937).

3. An increased ascorbic acid requirement to produce 'saturation' (Gander and Niederberger, 1936).

4. Abnormally low blood and serum ascorbic acid levels (Faulkner and Taylor, 1937; Rinehart, Greenberg, and Baker, 1936; Wortis, Liebman, and Wortis, 1938).

In seeking an explanation for the increased requirements in infection, an association with the accompanying leucocytosis has been suggested (Harris, 1937). This speculation is based on the observation that leucocytes contain a large amount of ascorbic acid (Stephens and Hawley, 1936). It is clear that in leukaemia a condition exists where the effect of a leucocytosis without infection can be studied. It is the purpose of this paper to report a series of investigations on the relation between the leucocyte count in leukaemia and the utilization of ascorbic acid, and to record further observations on the effect of large doses as a therapeutic measure.

#### *Methods*

All patients under investigation were given a carefully prepared diet containing approximately 30 mg. of ascorbic acid per diem. In order to establish a 'base line' an additional 25 mg. of ascorbic acid (half a Redoxon tablet) were given daily by mouth for nine days. For the remainder of the period under observation, the patients received 1,000 mg. of ascorbic acid (Redoxon powder) a day in divided oral doses of 500 mg. morning and evening. An exception was made in Case 2 (acute myeloblastic leukosis), who received 5,000 mg. of ascorbic acid in the first twenty-four hours after admission. This was given intravenously by the slow-drip method.

*Urine.* The excretion of ascorbic acid in the urine was estimated by the method of Harris and Ray (1935); for details of technique see Abbasy, Harris, Ray, and Marrack (1935), and Harrison (1937). Several investigators, notably Emmerie and van Eekelen (1934), van Eekelen and Heinemann (1938), and Scarborough and Stewart (1937), have raised objections to this method on the ground that other reducing substances interfere with the accurate determination of ascorbic acid. The quantity of these substances is trivial in proportion to the amount of ascorbic acid excreted with the large doses used in this series (van Eekelen and Heinemann, 1938).

*Blood.* Ascorbic acid values for whole blood and plasma were estimated by the method of Farmer and Abt (1935), as modified by Pijoan and Klemperer (1937), with the exception that 5 c.c. of whole blood or plasma were used with an equal amount of 10 per cent. trichloroacetic acid to precipitate the protein as suggested by Zilva (1937).

*Intradermal test.* The intradermal test for vitamin C deficiency, as reported by Rotter (1937), and modified for use in human subjects by Portnoy

and Wilkinson (1938), was tried during the course of this investigation. The test was fairly satisfactory in showing the trend of saturation, but did not prove sufficiently accurate for the purposes of the present communication.

### *Cases*

Ten patients from the Medical Professorial Unit wards in St. Bartholomew's Hospital were studied during this investigation. Two patients were suffering from acute and two from chronic leukaemic myelosis. Six other patients served as controls, as their diet before admission seemed adequate; they were afebrile, had normal total and differential leucocyte counts (5,000 to 10,600 per c.mm.), and were not acutely ill. The course followed by the control patients was in all respects similar to previously reported control results (Abbasy, Hill, and Harris, 1936; Archer and Graham, 1936), and for this reason only one case will be reported in detail as a basis for comparison. This case is particularly useful as a control, since she showed wide variations in her erythrocyte and platelet counts with little change in her leucocyte count.

*Case 1 (Control).* W. M., female, aged 57 years. Weight, 9 st. 1 lb. Idiopathic thrombocytopenic purpura (see Fig. 1). Admitted to hospital under the care of Professor L. J. Wits on 22nd March, 1938, with a history of purpura of six months' duration. The diet had been adequate. On admission there was bleeding from the ear and gums, with haematemesis and melaena. A diffuse purpuric rash was present, and the tourniquet test was markedly positive.

Blood count on admission: R.B.C. 3,300,000 per c.mm.; Hb. 67 per cent. (100 per cent. = 13.8 gm. per 100 c.c.); W.B.C. 10,400 per c.mm., with a normal differential count; platelets, 35,000 per c.mm. (Fonio); bleeding time (Dukes), more than thirty minutes.

The patient was given a transfusion of 300 c.c. of citrated blood on the fourth day after admission. She was then put on the ascorbic acid routine, and the daily excretion of ascorbic acid in the urine was estimated. During the period allowed for a 'base line' she excreted from 7 to 15 mg. of ascorbic acid a day. The initial whole-blood and plasma ascorbic acid values were 0.3 and 0.5 mg. per 100 c.c. respectively. Following the daily administration of 1,000 mg. of ascorbic acid, the urinary excretion rose to 53 mg. on the first, 118 mg. on the second, 208 mg. on the third, and 548 mg. on the fourth day. For the remainder of the period under observation the daily excretion varied from 520 to 712 mg. The plasma ascorbic acid rose to 1.4 mg. per 100 c.c. and that of the whole-blood to 0.9 mg. per 100 c.c., and remained fairly constant during the remainder of the forty days under treatment. The haemorrhage from the ear and the purpuric manifestations had subsided by the twelfth day. The tourniquet test was negative on the twenty-first day, and the bleeding time was then three minutes. At the time of discharge from the hospital the platelets had risen to 909,000 per c.mm.; the Hb. was 87 per cent.; the erythrocyte count was 3,990,000 per c.mm. and the leucocyte count 6,000 per c.mm.

In spite of a variation in the erythrocyte count between 2,400,000 and 3,990,000 and in the platelet count between 26,000 and 909,000, no significant variation in the ascorbic acid metabolism was observed.

*Case 2.* C. B., male, aged 48 years. Weight, 11 st. Acute myeloblastic leukaemia. Admitted to hospital under the care of Professor L. J. Witts on 17th February, 1938, with a history typical of acute leukaemia of twelve weeks' duration. His diet had been adequate, including fruit and vegetables. On examination, he was acutely ill with a temperature of 100° F. There

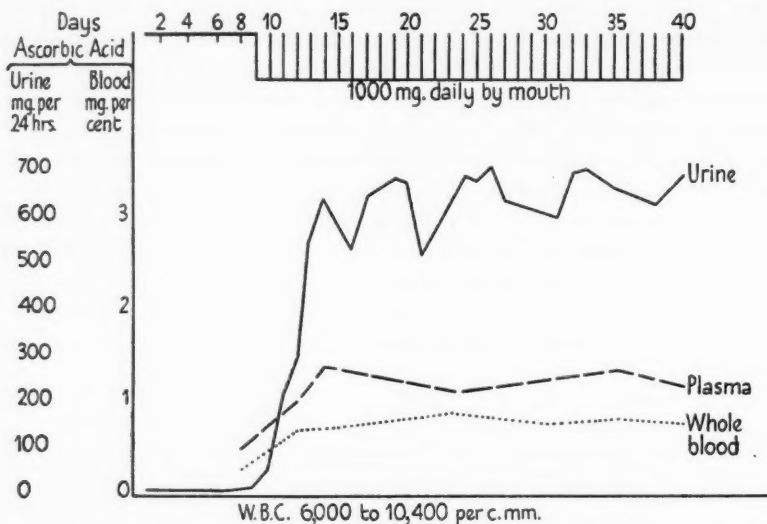


FIG. 1. Control patient (Case 1). The response to large doses of ascorbic acid.

was bleeding from the gums and nasal mucous membranes. The urine contained gross blood, and there were purpuric lesions over the arms and chest. The liver and spleen were palpable.

Blood count on admission: R.B.C. 1,370,000 per c.mm.; Hb. 27 per cent.; W.B.C. 185,000 per c.mm., with 83 per cent. myeloblasts; platelets, 27,400 per c.mm.; bleeding time, three minutes; tourniquet test, positive.

In the first twenty-four hours after admission the patient received 5,000 mg. of ascorbic acid given intravenously by the slow-drip method. For the next five days he was given 1,000 mg. daily by mouth. The urinary excretion of ascorbic acid was 418 mg. on the day of admission, 465 mg. on the fourth day, and 360 mg. on the fifth. The whole-blood ascorbic acid rose from 2.8 mg. per 100 c.c. on the second day to 3.5 mg. on the fifth; the plasma from 1.4 mg. to 1.9 mg. The leucocytes increased from 178,000 per c.mm. on the fourth day to 253,000 on the fifth day. No improvement was noted following the large doses of ascorbic acid. Bleeding from the gums continued, and epistaxis developed on the fourth day after admission. Death occurred on the sixth day. At autopsy the bone-marrow and organs showed myeloid infiltration, in which myeloblasts predominated.

*Case 3.* E. M., female, aged 16 years. Weight, 8 st. 7 lb. Acute myeloblastic leukaemia. Re-admitted to hospital under the care of Professor Ronald Christie on 27th April, 1938. At the time of her first admission in March 1938, a diagnosis of aleukaemic myelosis had been made, and this was confirmed by sternal puncture (smears showed 93 per cent. myeloblasts). The entire history was of sixteen months' duration. During this period the diet

had contained fruit and vegetables in abundance. On re-admission she was extremely pale and dyspnoeic, and the spleen was palpable 3 cm. below the costal margin. No haemorrhagic phenomena were noted.

Blood count on admission: R.B.C. 1,610,000 per c.mm.; Hb. 31 per cent.; W.B.C. 63,400 per c.mm., with 97 per cent. myeloblasts; platelets, 607,000 per c.mm.

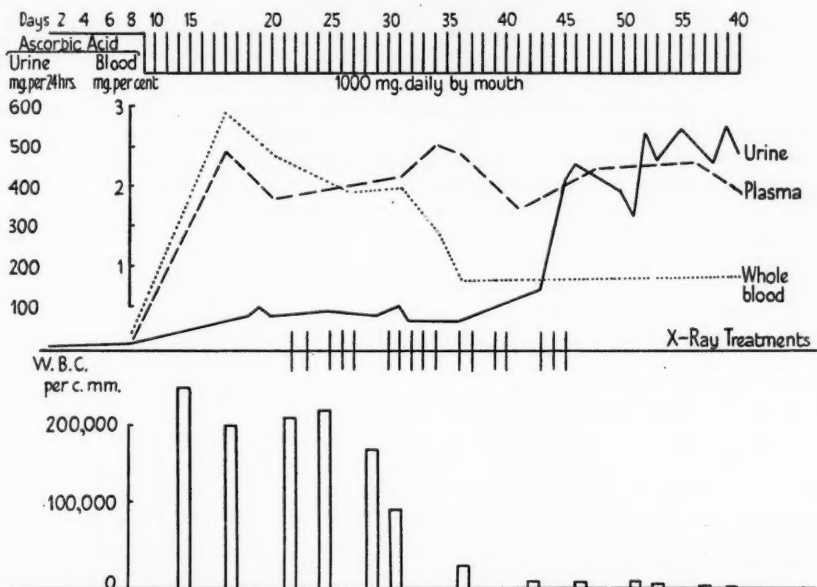


FIG. 2. Chronic leukaemic myelosis (Case 4). The response to large doses of ascorbic acid.

The routine for the administration of ascorbic acid was followed. During the control period she excreted from 4.5 to 6 mg. of ascorbic acid daily. The initial whole-blood and plasma ascorbic acid values were 0.55 and 0.4 mg. per 100 c.c. respectively. Following the daily administration of 1,000 mg. of ascorbic acid, there was no increase in the urinary excretion until the fourth day, when 200 mg. were recovered. The patient never became saturated and the daily excretion varied from 200 to 400 mg. during the remainder of the period under observation. The plasma ascorbic acid rose to 2.45 mg. per 100 c.c. and the whole-blood to 3.0 mg. on the fifth day, and remained fairly constant.

No improvement was noted, and the leucocyte count rose to 73,000 per c.mm., while the haemoglobin fell to 11 per cent. and the erythrocyte count to 950,000 per c.mm. After a period of observation lasting 40 days, ascorbic acid therapy was abandoned and transfusions were instituted, with only temporary improvement.

*Case 4.* J. C., male, aged 32 years. Weight, 10 st. 2 lb. Chronic leukaemic myelosis (see Fig. 2). Re-admitted to hospital under the care of Professor L. J. Witts on 12th December, 1937. A diagnosis of chronic leukaemic myelosis had been made on a previous admission in March 1937, and he had responded to radiotherapy. His illness dated from October 1936. During the entire course of his illness he had received a full diet

containing fruit and vegetables. At the time of re-admission to hospital, he complained of abdominal discomfort and weakness, but did not appear acutely ill. The liver edge was palpable and the spleen extended to a point 5 cm. above the crest of the ilium.

Blood count: R.B.C. 3,440,000 per c.mm.; Hb. 73 per cent.; W.B.C. 203,000 per c.mm., with 21 per cent. myelocytes; platelets, 722,000 per c.mm.; bleeding time, five minutes; tourniquet test, negative.

The patient followed the routine for the administration of ascorbic acid. During the control period, the urinary excretion of ascorbic acid varied from 10 to 14 mg. in twenty-four hours. Initial whole-blood and plasma ascorbic acid levels were 0.48 and 0.3 mg. per 100 c.c. respectively. Following the daily administration of 1,000 mg. of ascorbic acid, there was only a slight increase in the urinary excretion during the period of leucocytosis. The average excretion was in the neighbourhood of 100 mg. in twenty-four hours. The whole-blood ascorbic acid rose to 3 mg. per 100 c.c. and the plasma to 2.5 mg. on the eighth day after the large doses were given. There was no significant change in the leucocyte count during the ascorbic acid therapy alone. On the thirteenth day, splenic irradiation was started. Following this there was a rapid fall in the leucocyte count to a normal level and the spleen became impalpable. With the fall in the leucocyte count, the whole-blood ascorbic acid level fell below that of the plasma, which it had hitherto exceeded, and the unusually small excretion of ascorbic acid in the urine rose to the saturation level (50 per cent. or more).

*Case 5.* B. W., male, aged 42 years. Weight, 10 st. 2 lb. Chronic leukaemic myelosis (see Fig. 3). Re-admitted to hospital under the care of Professor Ronald Christie on 23rd April, 1938. At the time of his first admission in February 1937, a diagnosis of chronic myeloid leukaemia had been made. Following a course of X-ray therapy and blood-transfusion, he had been discharged much improved. He returned to work as a gardener, and his diet had been adequate, including more than an average amount of fruit and vegetables. On re-admission, he complained of anorexia, general malaise, and occasional attacks of vomiting. The spleen was palpable 7 cm., and the liver 2 cm., below the costal margin. No haemorrhagic phenomena were noted.

Blood count: R.B.C. 3,830,000 per c.mm.; Hb. 75 per cent.; W.B.C. 246,000 per c.mm., with 18 per cent. myelocytes; platelets, 490,000 per c.mm.; bleeding time, one and a half minutes.

The routine administration and investigation of ascorbic acid were followed. During the control period the urinary excretion of ascorbic acid varied from 13 to 18 mg. in twenty-four hours. The initial whole-blood and plasma ascorbic acid values were 0.42 and 0.3 mg. per 100 c.c. respectively. Following the administration of 1,000 mg. of ascorbic acid a day, the urinary excretion was 13 mg. on the first day, 15 mg. on the second, 18 mg. on the third, 55 mg. on the fourth, 90 mg. on the fifth, 300 mg. on the sixth, and 431 mg. on the seventh. Although the response was more marked than in Case 4, the urinary excretion did not rise to the usual saturation level during the period of leucocytosis. The whole-blood and plasma ascorbic acid rose to 2.5 and 2.35 mg. per 100 c.c. respectively on the eighth day. There was no significant variation in the leucocyte count during the treatment with ascorbic acid alone. On the ninth day, arsenic therapy was started with the daily administration of from 6 to 24 mg. of arsenic, in the form of arsenic trioxide. Following this the leucocyte count fell from 280,000 to 5,000 per c.mm. There was no demonstrable variation in the size of the spleen. With the

fall in the leucocyte count, the whole-blood ascorbic acid level fell below the plasma level. The plasma remained at a supra-liminal level during the remainder of the period under investigation, the 'critical level' for the saturated state being 1.4 mg. per 100 c.c. (Faulkner and Taylor, 1938). The urinary excretion of ascorbic acid rose to 720 mg. or more daily, following the fall in the leucocyte count.

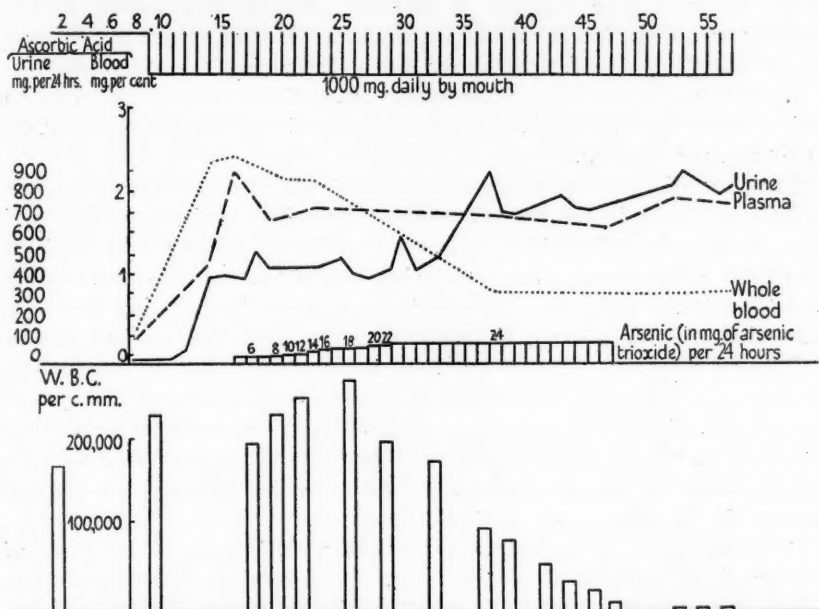


FIG. 3. Chronic leukaemic myelosis (Case 5). The response to large doses of ascorbic acid.

#### Discussion

When the four recognized criteria for vitamin C requirements were applied to the patients in the present investigation, the following results were obtained:

1. *Maintenance of 'minimal standard excretion'.* During the period provided for a 'base line', three patients suffering from leukosis (Cases 3, 4, and 5) and three of the control group had a daily urinary excretion of less than 13 mg. of ascorbic acid (the value usually taken as a 'minimum standard' excretion) (Abbasy, Harris, and Ellman, 1937). It may well be that the other control cases would have reached the minimal standard excretion if the control period had been longer.

2. *Response to test dose of ascorbic acid.* The daily administration of 1,000 mg. by the mouth in three cases of leukosis did not significantly increase urinary excretion of ascorbic acid during the first three days. In the control series the urinary excretion varied from 5 to 50 per cent. on the first day and had risen to 50 per cent. or more on the fourth day. In Case 2, another

patient with leukosis, 5,000 mg. of ascorbic acid were given intravenously and this led to the excretion of only 418 mg. in the urine. A normal individual would be expected to excrete at least 2,500 mg. (Wright, Lilienfeld, and MacLenathen, 1937).

3. *Ascorbic acid requirements to produce saturation.* From 500 to 4,000 mg. of ascorbic acid were required to saturate the control patients. In the patients with leukosis the amount required was obviously much greater, and in fact saturation was never achieved during the period of leucocytosis.

4. *Blood and serum ascorbic acid levels.* All patients, including the control series, showed low initial plasma and whole-blood ascorbic acid levels (0.15 to 0.7 mg. per 100 c.c.).

Thus, according to the first and fourth criteria, the patients with acute and chronic leukosis and the six controls showed an abnormally low level of vitamin C nutrition. This observation, although it may support those who believe that most of the population is in a 'suboptimal state', shows that these two criteria alone are of little or no value in detecting the more marked degrees of vitamin C deficiency. The other two criteria are in a different category. Judged by them, the controls behaved in a normal manner, for when given large doses of ascorbic acid (1,000 mg. daily) they became saturated within four days, with a urinary excretion of from 50 to 72 per cent. of the daily intake. The response of patients with leukosis was abnormal, for the saturation point was never reached, and the amount excreted in the urine was from 8 to 40 per cent.

It is apparent, therefore, that patients with leukosis are capable of retaining large amounts of ascorbic acid. It is reasonable to suppose that this is either stored or used. Before the administration of vitamin C, the whole-blood ascorbic acid in leukaemia is low, though higher than the plasma value. After the administration of vitamin C, the amount of substance in the blood in leukaemia which reduces the redox dye rises to a higher level than that which is found in the controls under comparable conditions. This excess bears a direct relationship to the number of circulating leucocytes, and no relationship to the number of erythrocytes or platelets, or to the size of the spleen. An increased storage of ascorbic acid by the leucocytes is in itself not sufficient to account for the very large amounts of reducing substance, for the amount in the plasma is also increased (Stephens and Hawley, 1936). If this reducing substance is indeed ascorbic acid—and the nature of the chemical test and the fact that the rise occurs after the administration of ascorbic acid make this appear probable—then it would seem that the excess of ascorbic acid in the blood is due not only to the increased storage on the part of the leucocytes, but also to a rise in the renal threshold for ascorbic acid. When the leucocyte count is reduced by therapeutic means the amount of reducing-substance in the whole-blood likewise falls, but the plasma value undergoes little change. Nevertheless, ascorbic acid now appears in the urine, as if the renal threshold had fallen. This change is not due to the effect of radiotherapy, as it also occurs following treatment

with arsenic. It would serve no useful purpose to theorize further on the metabolic significance of these findings.

The accompanying leucocytosis affords only a partial explanation of the increased usage of vitamin C in infection, which is seen also in infections not associated with a leucocytosis; increased metabolism is probably an additional factor. There was no significant fall in the leucocyte count when the patients were receiving large doses of ascorbic acid alone. These findings agree with those of Gingold (1937) and Thiel (1938), but do not confirm the therapeutic results claimed by Eufinger and Gaetgens (1936). The increase in the number of platelets noted in Case 1 might be credited to ascorbic acid therapy if spontaneous remissions in thrombocytopenic purpura were not so common; however, Thiel (1938) has claimed that ascorbic acid raises the platelet count. The haemorrhagic state associated with acute myeloblastic leukaemia was not affected by large doses of ascorbic acid.

#### *Summary*

1. Observations were made on the effect of large doses of ascorbic acid (1,000 mg. per diem) on a series of 10 patients; six served as controls, two had acute, and two chronic, leukaemia.

2. Following the administration of large doses of ascorbic acid, no improvement was observed in the two cases of acute, or in the two cases of chronic, leukaemia.

3. In leukaemia an excessive amount of ascorbic acid can be absorbed and retained, and the amount of ascorbic acid in the blood cells is increased. These abnormalities bear a direct relationship to the number of circulating leucocytes, and it is suggested that leucocytes absorb a large amount of ascorbic acid.

4. In leukaemia whole-blood contains more ascorbic acid than the plasma, and the whole-blood ascorbic acid falls below the plasma level coincidentally with the fall in the leucocyte count.

5. The increased requirements for vitamin C in infection are probably partly due to the accompanying leucocytosis.

This work was carried out while the author was an exchange fellow in Medicine at St. Bartholomew's Hospital from the Pennsylvania Hospital, Philadelphia, Pennsylvania.

It is my pleasant duty to thank Professors L. J. Witts and Ronald Christie and Dr. R. Bodley Scott for permission to study patients under their care and for encouragement and help in the preparation of this paper. I am also indebted to Miss M. Abrahams for the supervision and preparation of the diets used in this investigation, and to Miss F. E. Evans and Miss M. Watkin, ward sisters, for their careful collection of the urine samples. My thanks are also due to the Roche Products Ltd., London, for their generous supplies of Redoxon.

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# PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1938

## THIRTY-SECOND ANNUAL GENERAL MEETING

THE THIRTY-SECOND ANNUAL GENERAL MEETING was held in Bristol on Friday and Saturday, June 3 and 4, 1938, in the Physics Theatre of the University. The attendance book was signed by 159 members. The proceedings began at 10 a.m.

*The Treasurer*, Dr. H. Letheby Tidy, was in the Chair in the absence through ill health of the President, Sir Robert W. Philip.

*Death of Honorary Member.* The death of Dr. George R. Parker, who had been in the Chair at the meeting in Bristol in 1924 was reported, and members expressed their regret by standing in silence for a minute.

*The Minutes* of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

*The Treasurer* presented the Annual Accounts, which showed a balance of £326 10s. 6d. Expenses had been smaller during the past year, and the financial situation of the Association was very satisfactory.

*Selection of Place of Meeting for 1939.* A letter was received from Dr. T. L. Hardy on behalf of the Birmingham members, inviting the Association to meet in Birmingham in 1939. This invitation was cordially accepted.

*Quarterly Journal of Medicine.* The Secretary reported that Dr. A. G. Gibson had resigned from the posts of Editor and Secretary of the Editorial Board; that Professor J. A. Ryle had resigned from the post of Editor; and that Dr. A. M. Cooke had been appointed Secretary to the Editors in succession to Dr. A. G. Gibson. The meeting expressed its appreciation of the services of Dr. A. G. Gibson for the *Quarterly Journal of Medicine* right from the time of its foundation. The Editors had recommended the appointment of Professor O. L. V. S. de Wesselow as Editor, and his appointment was unanimously approved by the meeting.

### *Election of Officers*

*President.* Professor J. A. Nixon was unanimously elected President. On his election he took the Chair and thanked the Treasurer for opening the Meeting. He expressed the thanks of the Association to the Retiring President, Sir Robert W. Philip, and it was unanimously decided to send Sir Robert a message of sympathy and wishes for a speedy return to his usual activity.

Election of Officers, Executive Committee, Honorary Members, Extra-Ordinary Members, and Ordinary Members then followed.

### *Executive Committee*

*President.* Professor J. A. Nixon.

*Treasurer.* Dr. H. Letheby Tidy.

*Secretary.* Professor L. J. Witts.

### *Members for England:*

Dr. J. Crighton Bramwell.

Dr. A. Feiling.

Dr. F. G. Hobson.

Dr. C. E. Lakin.

Dr. H. J. Starling.

Professor O. L. V. S. de Wesselow.

*Members for Scotland :*

Dr. G. A. Allan.  
 Professor L. S. P. Davidson.  
 Dr. A. Goodall.

*Members for Ireland :*

Dr. R. Marshall.  
 Dr. R. H. Micks.  
 Dr. S. I. Turkington.

*Honorary Members :*

Sir Robert W. Philip (President 1937-38).  
 Dr. A. G. Gibson (Secretary to the Editors of the *Quarterly Journal of Medicine*, 1907-37).

*Extra-Ordinary Members :*

Dr. C. Bolton.  
 Sir J. Charlton Briscoe.  
 Dr. L. Findlay.  
 Dr. W. E. Foggie.  
 Professor John Hay.  
 Dr. T. Stacey Wilson.

*New Members :*

Edward Rowan Boland, F.R.C.P., Assistant Physician, Guy's Hospital.  
 Gerald Cecil Dockeray, M.D., Physician, Dr. Steevens' Hospital, Dublin.  
 Charles Sydney Douglas Don, M.D., Assistant Physician, Manchester Royal Infirmary.  
 John Callis Hawksley, M.D., Assistant Physician, University College Hospital.  
 Ian George Wilson Hill, F.R.C.P.E., Lecturer in Therapeutics, University of Edinburgh.  
 Ronald Epey Lane, M.R.C.P., Assistant Physician, Salford Royal Hospital.  
 Hugh Leslie Marriott, M.D., Assistant Physician, Middlesex Hospital.  
 Ronald Edward Smith, M.R.C.P., Medical Officer, Rugby School.  
 Douglas Stuart Stevenson, M.B., Assistant Physician, Western Infirmary, Glasgow.  
 Clifford Wilson, D.M., First Assistant, Medical Unit, London Hospital.

## SCIENTIFIC BUSINESS

*Friday Morning*

1. DR. C. J. McSWEENEY described his *Experiences with the Bragg-Paul Pulsator* in the treatment of 37 cases of respiratory paralysis, all except one (which was due to anterior poliomyelitis) being post-diphtheritic in origin. The pulsator satisfactorily maintained respiration for periods varying from five to sixteen days. No interference with the routine management, nursing, or treatment of patients was encountered, all the post-diphtheritic cases being nasally fed for a co-existent pharyngeal paralysis while in the pulsator. The pulsator had also been used for re-starting respiration reflexly arrested during a tracheotomy and during prolonged brain operations.

PROFESSOR R. V. CHRISTIE compared the Bragg-Paul Pulsator favourably with the Drinker apparatus, but DR. A. A. MONCRIEFF said that it had the theoretical disadvantage of working on the chest wall rather than the diaphragm and in practice the amplitude of respirations might be too shallow. DR. A. M. COOKE discussed the technique of artificial respiration in the intervals out of the apparatus.

2. DR. F. H. YOUNG spoke on *Multiple Cystic Disease of the Lungs*. An account was given of 13 cases which it was claimed are examples of this condition. The condition is silent until infection of the cystic areas develops. When they have once become infected the patient is never entirely free of symptoms. The symptoms are mainly similar to bronchiectasis, but offensive sputum does not seem to occur unless there is an associated bronchiectasis. The prognosis for life is good, judged by the history of the cases, as, out of 13, two have existed for at least thirty years and two only have died, one as the result of surgery and the other of acute leukaemia. Unless urgent symptoms occur, surgery should not be advised until the mortality from lobectomy becomes negligible.

PROFESSOR RYLE, SIR M. CASSIDY, and DR. PARKES WEBER made brief comments, and DR. A. E. GOW mentioned a patient with congenital cystic disease of the lungs who died of spontaneous pneumothorax.

3. DRS. DONALD HUNTER and R. R. BOMFORD (introduced) described *Poisoning by Methyl Mercury Compounds* in industry. Four cases were described of poisoning by inhalation of fungicides containing methyl mercury compounds. Salivation, stomatitis, tremor, and erethism were absent, but the nervous system was involved in a unique way. There was severe generalized ataxia, dysarthria, and gross constriction of the visual fields, memory and intelligence being unaffected. In one case re-education for more than twelve months led to improvement in gait, in the use of the hands and in speech. Rats and monkeys exposed to the vapour of methyl mercury iodide became ataxic. Histological studies by DR. DOROTHY RUSSELL showed myelin degeneration in the peripheral nerves, and particularly in the posterior roots and dorsal columns. A cinematograph film was shown to demonstrate the disability in one patient and in experimental animals.

The communication was discussed by DRS. PARKES WEBER, CARLILL, BURROW, and MONCRIEFF, the last eliciting the information that the success of treatment was due to constant encouragement by the attendants and not to the banana diet which had figured so prominently on the screen.

4. DR. J. C. SPENCE discussed the *Clinical Effects in Young Children of Tuberculous Infection*. In 132 children under the age of three years the source of tuberculous infection was traced in 62 to parents or other human sources. He used his material chiefly to confirm Wallgren's views of the sequence of clinical events which follows the primary infection. The infrequency of tuberculous erythema nodosum in early infancy compared with later childhood was noted. He supported the view that if tuberculous meningitis were to occur it would appear between the third and sixth month following infection, except in cases with a tuberculous bone lesion when it might appear later. He drew attention to the tendency for tuberculous dactylitis to be a symmetrical lesion in young infants affecting the same bones of both hands and feet.

5. DR. R. BODLEY SCOTT (introduced by DR. A. E. Gow), discussing *The Sarcoidosis of Boeck*, said that the sarcoid of Boeck has been familiar to dermatologists for many years, but only recently has the disease been recognized as a generalized morbid state in which cutaneous lesions are present in less than 50 per cent. of cases. The histology of all the lesions is identical and has been familiar for forty years as hyperplastic or endothelial tuberculosis, although evidence that sarcoidosis is due to infection with *M. tuberculosis* is unconvincing. From the morbid anatomical standpoint it must be regarded as a reticulosis. The main clinical manifestations are lymphadenopathy and splenomegaly; skin infiltrations, which may be of four types, miliary lupoid, lupus pernio, angio-lupoid, and erythrodermie sarcoidique; osteitis multiplex of the digits; and irido-cyclitis. Pulmonary changes are present in 80 per cent. of cases and consist of enlargement of mediastinal and hilar lymph nodes and miliary infiltrations. Parotid and lachrymal gland enlargement is common, and there is good evidence that the uveo-parotid syndrome is only a clinical variant of sarcoidosis. The disease runs a benign course over many years and has a tendency to spontaneous retrogression and cure.

DR. IZOD BENNETT described how he and his colleagues had sought and found a number of cases of this disease by investigating patients with chronic iridocyclitis, and PROFESSOR ELLIS described a case in which ophthalmoscopic examination revealed changes identical with tubercles of the choroid.

6. LORD DAWSON, when *Illustrating Undifferentiated Lymphatic Tumours*, described cases which, although showing widely differing clinical symptoms, were nevertheless examples of the same disease process, reticulum cell sarcoma. On the one hand the symptoms were related to toxæmia, while those of the second group were dependent on the local manifestations. He described in detail two cases in both of which pathological examination of glands removed during life showed surprising results, early biopsy indicating hyperplastic changes only. Until late in the course of the first case the blood picture remained normal, and but for that the patient would not have lived long enough to develop paraplegia. On post-mortem examination there were widespread enlargement of glands and diffuse infiltration of the spinal cord and bone-marrow. The pathological report then made was reticulo-sarcoma. In the second case, one of the glands removed at operation evoked a difference of opinion amongst three pathologists, two of whom agreed that it could be reticulum sarcoma. That there must be some link between these two cases was evident, and the proposition was put forward that the same agent, possibly a virus, produced varying results by its selection and direction of spread in different individuals. The connecting link was

still to be found, but the resulting chain of events was determined by the reaction of the individual's reticulo-endothelial system to attack by disease.

PROFESSOR McNEE mentioned the analogous condition of lymphosarcoma of the spleen, which could be completely cured in the early stages by splenectomy. DR. PARKES WEBER suggested that it was simplest to diagnose all the obscure reticulo-endothelial maladies as Hodgkin's disease, but DR. TIDY indicated that the real difficulty lay in separating them in the early stages from transient simple inflammatory changes.

7. DR. R. J. A. BERRY (introduced by PROFESSOR J. A. NIXON) described *Cerebral Malformations and their Clinical Consequences*. From a collection of 146 defective and 106 normal brains there were exhibited and described six normal brains, showing the growth in size and weight of the normal brain between the ages of 2 days and 6 years. Contrasted with these were six defective brains from 5.5 years to 24.1 years. The defective brains were from 20 per cent. to 30 per cent. smaller than normal—hence the mental deficiency. A further series of six defective brains illustrated the frequency of teratological deformities, those shown being cerebral agenesis; absence of the corpus callosum; ossification of the dura mater; gross hydrocephalus; megalencephaly; and microgyria. Such cerebral malformations of size, weight, and structure were clearly incompatible with a normal neurological functioning and hence the probability of a simulation of disease processes in the nervous system.

2 p.m. to 3 p.m.

Clinical Cases in the Royal Fort House and Demonstrations in the Physics Laboratory.

3 p.m. Afternoon Session

1. DR. P. MANSON-BAHR described *Amoebic Infection of the Skin and Subcutaneous Tissues*. The invasion of the skin by *Entamoeba histolytica* has been noted on several occasions, but is apparently very rare. The lesions produced are both severe and extensive. Ulceration of the skin of the abdominal wall with infiltration of the subcutaneous tissues occurred in a patient in whom a colostomy had been performed for supposed carcinoma of the rectum. The patient, an ex-soldier, was found to be infected with *Entamoeba histolytica* which had escaped from the bowel. The curative effect of emetine injections was extremely rapid. The recognition of amoebiasis in this patient led to the discovery in St. Mark's Hospital of a second and even more extensive case of ulceration of the buttocks.

2. DRS. E. R. CULLINAN and E. WITTKOWER (introduced) described some *Clinical Aspects of Ulcerative Colitis*, suggesting that the disease attacked individuals of abnormal temperament.

PROFESSOR RYLE doubted the validity of the psychological data and the control observations in a chronic disease such as ulcerative colitis, but SIR EDMUND SPRIGGS said that Dr. Cullinan's observations were in harmony with his own large experience, inasmuch as ulcerative colitis rarely developed in successful people. DR. TIDY discussed the general management of these cases.

3. SIR EDMUND SPRIGGS gave a demonstration of *Diverticulosis in the Rat and in Man*, by kind permission of D. M. LUBBOCK, W. THOMSON, and R. C. GARRY. The lesions in the bowels of rats had been observed during a nutritional research in the Rowett Institute, Aberdeen. The acinar and cystic formations appear to be heterotopic and different from the diverticula hitherto described in man, the horse, and the sheep. In man, so far as present observations go, in a piece of colon of which an extensive area was observed radiologically in the prediverticular state, the circular muscle was in bundles and less continuous than in the normal gut. Between the bundles the submucosa filled up the spaces, with a corresponding protrusion of the mucosa towards the peritoneal surface at some areas, and at others little or no such protrusion. The gaps between the bundles of circular masses were as evident under a taenia as away from it. At the next stage of formed pouches the lining mucosa was as thick in the pouches; here the circular muscle bundles were thicker. Slides of radiograms, sections by O. A. Marxer and S. W. Patterson, and slides of the later diverticulitis by Professor M. J. Stewart illustrated the above points. The help of members was asked in obtaining early material.

4. DR. F. AVERY JONES described *The Treatment of Recurrent Haemorrhage from Peptic Ulceration*. Although there is still much difference of opinion about the mortality of gastro-duodenal bleeding, there is no dispute about the gravity of repeated haemorrhage. In a series from the same hospital five years ago, there was a mortality

of 41 per cent. in cases of recurrent haematemesis. In this series of 47 cases, bleeding recurred in 13, of which six were severe cases. One patient died, but has since been shown to have had ulcer cancer. The patients were treated by a liberal diet from the onset, and were given transfusions to maintain the haemoglobin at about 40 per cent. Large drip transfusions were given in five cases. Slides were shown to demonstrate the absence of or only slight rise in blood pressure when 1,200 to 3,000 c.c. of blood were injected at the rate of 100 to 120 c.c. an hour. The use of drip transfusions was recommended in the treatment of severe recurrent gastro-duodenal haemorrhage.

5. DR. T. IZOD BENNETT spoke of the *Observations on Blood-volume in Gastric Haemorrhage* which had been made during the last three years in the Courtauld Research Wards of the Middlesex Hospital by himself and his co-workers, Professor Samson Wright, Dr. F. Lee-Lander, and Dr. James Dow. Without observations of the total volume of red cells in the blood it was impossible to determine how much blood had been lost, or whether bleeding was arrested, or whether further haemorrhage had occurred. Observations of the haemoglobin were frequently extremely misleading and often dangerously so. Graphs were shown demonstrating these points and showing how the restoration of plasma would bring about a fall in the haemoglobin, simultaneously with an improvement in the patient's general condition. The speaker agreed that transfusion was frequently essential for the preservation of life, but emphasized his opinion that the transfusion of a large volume of blood might easily provoke further haemorrhage, and showed how observations on the blood-volume demonstrated that, after a severe haemorrhage, a large blood transfusion could produce an increase in the blood-volume above the full normal figure long before the cell-volume had been restored.

PROFESSOR RYLE confirmed the value of blood-volume determinations and suggested that the frequency of recurrence in Dr. Avery Jones' patients might be due to too vigorous transfusion. Members were somewhat abashed at the suggestion that it was hardly possible to treat, or at any rate to transfuse, cases of gastro-duodenal bleeding without blood-volume examinations, but Dr. TIDY was brave enough to state that he was able to judge the needs of the patient by clinical examination and haemoglobin estimation. DR. G. GRAHAM was of the same opinion: when a patient was very ill he should be transfused and there was little danger of increasing the blood-volume, as one did not try to maintain the haemoglobin higher than 60 or 70 per cent. DR. GRAHAM believed in immediate transfusion, in contrast to DR. CULLINAN who suggested waiting 24 hours. DR. LESCHER had used repeated transfusions of 500 c.c. with success. PROFESSOR WITTS pointed out that there was no evidence that treatment by feeding and transfusion had increased the number of recurrences; in patients treated at St. Bartholomew's Hospital before and after this régime was introduced the percentage of recurrences was identical, but the mortality had abruptly fallen. Finally, DR. PLATT argued that there was no physiological reason why an increased blood-volume should raise either the blood-pressure or the tendency to bleed. DRS. COLE, K. D. WILKINSON, MANSON-BAHR, HILTON, and BARNES also spoke.

6. DR. HUGH BARBER and DR. G. R. OSBORN (introduced) discussed the *Morbid Anatomy of a Case of Catarrhal Jaundice*. The lesions in a man who died as the result of a fall on the seventh day of jaundice were demonstrated. It was concluded to be a sporadic case of acute infective jaundice, which condition was epidemic in the district. There was mucus in the duodenum, but no inflammatory changes there or in the bile passages. The liver showed hepatitis.

PROFESSOR MCNEE emphasized the value of addition to knowledge of the pathology of simple jaundice, and PROFESSOR RYLE and DR. R. E. SMITH made some clinical observations. The discussion then wandered to inoculation jaundice, DR. MANSON-BAHR mentioning jaundice after immunization against yellow fever, and PROFESSOR L. G. PARSONS describing the same phenomenon after immunization against measles, again after a long latent period. PROFESSOR HARTFALL produced evidence that injections of gold sensitized patients to infection with simple jaundice.

#### Annual Dinner

The Dinner was held in the Great Hall of the University on Friday, June 3, at 7.30 p.m. The President, PROFESSOR J. A. NIXON, was in the Chair. The Official Guests included the Lord Bishop of Bristol, the Lord Mayor, the Vice-Chancellor of the University, and the Professor of Physics. There were present 107 members and guests.

*Saturday, 10 a.m., Morning Session*

1. DR. R. PLATT made *Observations on the Course of Bright's Disease*. In following up a large number of cases of renal disease some interesting facts had arisen. One case of acute nephritis which recovered was seen eight years later, the patient being then aged 32, as simple hypertension without albuminuria or renal insufficiency. Many cases of nephrosis appeared to run a very mild course and remained for years in fairly good health, with copious albuminuria but no symptoms. Though the current accounts of hypertension described a long benign phase preceding the malignant or renal phase, such cases were hardly ever encountered. Practically all those with renal involvement had renal insufficiency when first seen.

DRS. STOTT, ELLIS, PARKES WEBER, and CLIFFORD WILSON took part in the discussion.

2. DR. K. D. WILKINSON described *Hypertensive Encephalopathy* as seen in four cases of hypertension without renal involvement. Of two in children, one ended fatally and was due to a suprarenal tumour. The two in adults were characterized by fits, headache, and fairly prolonged unconsciousness, with papilloedema. Treatment with hypertonic rectal saline resulted in a rapid amelioration of symptoms and a return to work. It was considered that both the papilloedema and the symptoms in such cases were a result of cerebral oedema.

DR. TIDY described the occurrence of encephalopathy without hypertension in urticaria, and DR. MCALPINE mentioned the success of intravenous salyrgan in a refractory case when other remedies had failed. DRS. PARKES WEBER, H. EVANS, ELLIS, and L. G. PARSONS also spoke.

3. DR. J. M. O'DONOVAN gave an account of a case presenting *Bence Jones' Proteinuria* without X-ray evidence of bony change. The serum-calcium was raised and the plasma-phosphorus normal. The patient went rapidly downhill, and death was due to acute uraemia. The case was regarded as a myelomatosis sufficiently acute to be fatal before bony changes became visible.

DR. PARKES WEBER, apologizing amidst cheers for speaking too often, suggested that the osteophytes might be due to amyloid change and quoted chapter and verse of the ancient and modern literature on this interesting disease. DR. DONALD HUNTER accused the secretary of two misprints in a six-word title, but the latter was exonerated by PROFESSOR O'DONOVAN, who confessed to having hyphenated the name of Bence Jones and to having written 'proteosuria'. DR. TIDY congratulated Professor O'Donovan on being the author of the first communication from Cork. DR. CHARLES and SIR E. SPRIGGS also spoke.

4. DR. A. W. SPENCE described *The Effects of Substitution Therapy in Pituitary Cachexia*. The case of a patient suffering from pituitary cachexia due to a chromophobe adenoma which was removed 13 months previously was described. Daily injections of thyrotropic hormone (from pig anterior pituitary gland) caused an increase in basal metabolism from -30 per cent. to +57 per cent., but in spite of continued treatment, the rate subsequently fell to -44 per cent. Serum obtained from the patient while he was in the thyrotropic-resistant state was shown to possess antithyrotropic properties, in that it inhibited the action of thyrotropic hormone when both were injected into guinea-pigs. The basal metabolic rate did not rise again on injection of thyrotropic hormone from another source (ox), but rose to the normal level on the administration of thyroid. While he was receiving thyrotropic hormone, his general condition improved to a certain extent. Before treatment achlorhydria was present, but while the patient was receiving thyrotropic hormone increasing amounts of acid were secreted.

PROFESSOR WITTS commented on the relatively disappointing effects of this expensive form of therapy, and he also invited comments on the stiffness of the muscles of the lower extremities, which had been an outstanding symptom in this man. DRS. LAKIN and A. P. THOMSON then reported having seen the same thing in persons with pituitary disease, the stiffness being confined to the legs and being unattended by alteration in the reflexes or in the blood chemistry. PROFESSOR NAISH also spoke.

5. DR. L. ABRAHAMSON described two cases of *Hypochromic Anaemia in Males with Dysfunction of the Pituitary Gland*. In the first, aged 25, a blood count showed red cells 4 millions per c.mm., white cells 3,600 per c.mm., haemoglobin 32 per cent. There was achlorhydria. The nails were markedly spoon-shaped. Dysfunction of the pituitary gland was suggested by the extent and distribution of body fat, scantiness of hair on

the face, the appearance of the pubic hair, high-pitched voice, low basal metabolic rate ( $-22$  per cent.), and a high sugar tolerance. Administration of iron, with thyroid, had resulted in improvement of the blood condition to a red-cell count of over 6 million with haemoglobin 102 per cent. In the second man, aged 24, red cells were 4,040,000 per c.mm., haemoglobin 39 per cent., white cells 4,600 per c.mm. There was no free hydrochloric acid in the stomach. Body fat and pubic hair showed feminine distribution, hair scanty on face, shaving having commenced at age of 23. The blood-sugar curve was of the lag type, basal metabolic rate  $+20$  per cent. The blood-pressure was 138 mm. systolic, 80 mm. diastolic. Rapid improvement followed the administration of iron.

PROFESSORS SIR W. LANGDON-BROWN and L. G. PARSONS commented on the erythrocytosis during treatment, the latter indicating that it was not uncommon during treatment of an iron-deficiency anaemia. There was a loud 'No!' from the direction of PROFESSOR ELLIS when the opener invited agreement that these were undoubted examples of pituitary disease.

6. DR. H. M. SINCLAIR (introduced by PROFESSOR R. A. PETERS) discussed the *Value of Estimation of Vitamin B<sub>1</sub> in Blood*. The factors which tend to produce deficiency of vitamin B<sub>1</sub> were outlined. Firstly, since the requirement of the vitamin is proportional to the metabolism, deficiency will arise when the diet has a high energy value (particularly carbohydrate), but is low in vitamin B<sub>1</sub> or when the requirement is increased by muscular work, pregnancy, fever, or hyperthyroidism. Secondly, failure to assimilate the vitamin may arise from failure of absorption (owing to achlorhydria or disorders of the gut), from destruction by alkali in the gut, or from failure to phosphorylate it. These considerations were illustrated with the results of 200 estimations of the apparent amount of vitamin B<sub>1</sub> in blood (performed by a modification of Schopfer's method, using the fungus *Phycomyces*).

PROFESSOR PETERS said that he had recently found evidence that phosphorylation of the B vitamins occurred in the liver and this might have important clinical bearings. It was apparent that the audience had seen a new light, but was too dazzled by the conceptions of phosphorylation and adrenal control over absorption to say very much. Nevertheless, PROFESSOR ELLIS very appositely brought forward a case of polyneuritis and oedema developing immediately after removal of a cortical tumour of the adrenal and responding poorly to vitamin B<sub>1</sub>. DR. SINCLAIR indicated that this was just what might have been expected on Verzar's theories. DR. D. HUNTER also spoke.

2 p.m. to 3 p.m.

Clinical Cases in the Royal Fort House and Demonstrations in the Physics Laboratory.

### 3 p.m. Afternoon Session

1. MR. RENDLE SHORT (introduced by PROFESSOR C. BRUCE PERRY) related cases of *Long-standing and Intractable Sciatica* in which relief had been given by dividing a tense band of fascia pressing on the sciatic nerve, where it emerges from the sacro-sciatic foramen. Anatomical specimens were demonstrated. The operation was simple, but the method was only suitable when there is muscular wasting and long continued pain.

2. DR. G. D. KERSLEY (introduced by PROFESSOR L. J. WITTS) divided *Sciatic Pain*, which was the reason for admission of 8 per cent. of a recent series of cases to the Bath Royal National Hospital for Rheumatic Diseases, into that due to direct involvement of the nerve path and that referred especially from the posterior sacro-iliac ligaments and gluteal region. The latter was the predominant cause in 20 of the last 30 cases seen. Among the remainder the following diagnoses were made: two ankylosing spondylitis, two protruding intervertebral disk, two osteoarthritis, one tumour of the cauda equina, one partial subluxation in the lumbar region, one sacro-iliac strain, and one Paget's disease. DR. KERSLEY outlined the routine treatment employed, giving the results and showing X-rays of intrathecal lipiodol examination used only in the intractable cases, mentioning the value of laminectomy and deep X-rays in such cases, and asking for opinions on intrathecal alcohol injection.

3. DR. J. E. A. O'CONNELL (introduced by DR. C. M. HINDS HOWELL) described *Sciatica due to Prolapse of an Intervertebral Disk*. The work leading to the recognition of this lesion was summarized and its pathology and clinical features described. It was pointed out that there was little to differentiate such cases from other sciaticas. A history of preceding trauma and a raised cerebrospinal fluid protein might be helpful,

but radiography following the intrathecal injection of 5 c.c. of lipiodol was all important. In spite of prejudice felt against this procedure, large series of cases in which it had been carried out without ill effect were now on record. Treatment should be excision of the tumour—laminectomy would often be inadequate. It was urged that this lesion be borne in mind in all cases of persistent sciatic pain.

SIR WILLIAM WILLCOX commented on the value of X-rays in diagnosis; in treatment the motto should be 'Safety First'. DR. A. FEILING mentioned as additional factors of sciatica, sacralization of the fifth lumbar vertebra and intrathecal inflammation of the nerve roots—the latter being associated with a high protein level and often cells in the cerebrospinal fluid. DR. R. C. CLARKE said that in true sciatica the ankle-jerk was always lost, but this statement was promptly denied by Dr. Feiling. DR. CLOAKE had found fever-therapy beneficial at times. All the speakers deprecated the injection of alcohol in a non-malignant lesion such as sciatica.

At the conclusion of the meeting SIR WILLIAM WILLCOX proposed a hearty vote of thanks to the Bristol members for their hospitality, congratulating them on the success of the meeting and mentioning especially the services of the President, PROFESSOR J. A. NIXON; the Local Secretary, PROFESSOR C. BRUCE PERRY; and the Dinner Secretary, Dr. R. C. CLARKE. This was carried with acclamation.

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